NOVEL ISOXAZOLINE AND ISOXAZOLE FIBRINOGEN RECEPTOR ANTAGONISTS

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This invention relates to novel isoxazolines and isoxazoles which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex or the vitronectin receptor, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

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(57) Abstract

This invention relates to novel isoxazolines and isoxazoles which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex or the vitronectin receptor, to pharmaceutical compositions containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

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TITLE

Novel Isoxazoline and Isoxazole Fibrinogen Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel isoxazolines and isoxazoles which are useful as antagonists of the platelet glycoprotein IIb/IIIa fibrinogen receptor complex, to pharmaceutical compositions, including those for intranasal administration, containing such compounds, processes for preparing such compounds, and to methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

BACKGROUND OF THE INVENTION

Hemostasis is the normal physiological process in which bleeding from an injured blood vessel is arrested. It is a dynamic and complex process in which platelets play a key role. Within seconds of vessel injury, resting platelets become activated and are bound to the exposed matrix of the injured area by a phenomenon called platelet adhesion. Activated platelets also bind to each other in a process called platelet aggregation to form a platelet plug. The platelet plug can stop bleeding quickly, but it must be reinforced by fibrin for long-term effectiveness, until the vessel injury can be permanently repaired.

Thrombosis may be regarded as the pathological condition wherein improper activity of the hemostatic mechanism results in intravascular thrombus formation. Activation of platelets and the resulting platelet aggregation and platelet factor secretion has been

associated with a variety of pathophysiological conditions including cardiovascular and cerebrovascular thromboembolic disorders, for example, the thromboembolic disorders associated with unstable angina, myocardial infarction, transient ischemic attack, stroke, atherosclerosis and diabetes. The contribution of platelets to these disease processes stems from their ability to form aggregates, or platelet thrombi, especially in the arterial wall following injury.

Platelets are activated by a wide variety of agonists resulting in platelet shape change, secretion of granular contents and aggregation. Aggregation of platelets serves to further focus clot formation by concentrating activated clotting factors at the site of injury. Several endogenous agonists including adenosine diphosphate (ADP), serotonin, arachidonic acid, thrombin, and collagen, have been identified. Because of the involvement of several endogenous agonists in activating platelet function and aggregation, an inhibitor which acts against all agonists would represent a more efficacious antiplatelet agent than currently available antiplatelet drugs, which are agonist-specific.

Current antiplatelet drugs are effective against only one type of agonist; these include aspirin, which acts against arachidonic acid; ticlopidine, which acts against ADP; thromboxane A_2 synthetase inhibitors or receptor antagonists, which act against thromboxane A_2; and hirudin, which acts against thrombin.

Recently, a common pathway for all known agonists has been identified, namely platelet glycoprotein IIb/IIIa complex (GPIIb/IIIa), which is the membrane protein mediating platelet aggregation. A recent review of GPIIb/IIIa is provided by Phillips et al. *Cell* (1991) 65: 359-362. The development of a GPIIb/IIIa antagonist represents a promising new approach for antiplatelet therapy.

GPIIb/IIIa does not bind soluble proteins on unstimulated platelets, but GPIIb/IIIa in activated platelets is known to bind four soluble adhesive proteins, namely fibrinogen, von Willebrand factor, fibronectin, and vitronectin. The binding of fibrinogen and von Willebrand factor to GPIIb/IIIa causes platelets to aggregate. The binding of fibrinogen is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence which is common to the adhesive proteins that bind GPIIb/IIIa.

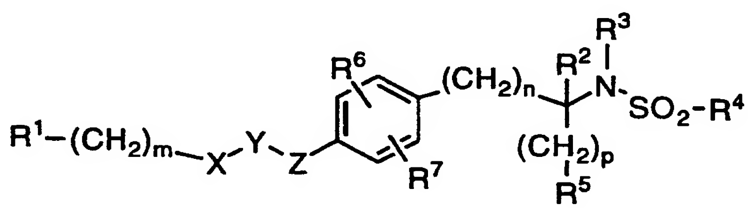
In addition to GPIIb/IIIa, increasing numbers of other cell surface receptors have been identified which bind to extracellular matrix ligands or other cell adhesion ligands thereby mediating cell-cell and cell-matrix adhesion processes. These receptors belong to a gene superfamily called integrins and are composed of heterodimeric transmembrane glycoproteins containing α- and β-subunits. Integrin subfamilies contain a common β-subunit combined with different α-subunits to form adhesion receptors with unique specificity. The genes for eight distinct β-subunits have been cloned and sequenced to date.

Two members of the β1 subfamily, α4/β1 and α5/β1 have been implicated in various inflammatory processes. Antibodies to α4 prevent adhesion of lymphocytes to synovial endothelial cells *in vitro*, a process which may be of importance in rheumatoid arthritis (VanDinther-Janssen et al., J. Immunol., 1991, 147:4207). Additional studies with monoclonal anti-α4 antibodies provide evidence that α4/β1 may additionally have a role in allergy, asthma, and autoimmune disorders (Walsh et al., J. Immunol., 1991, 146:3419; Bochner et al., J. Exp. Med., 1991 173:1553; Yednock et al., Nature, 1992, 356:63). Anti-α4 antibodies also block the migration of leukocytes to the site of inflammation (Issedutz et al., J. Immunol., 1991, 147:4178).

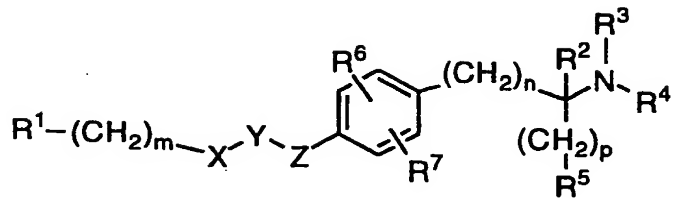
The α_v/β_3 heterodimer, commonly referred to as the vitronectin receptor, is another member of the β_3 integrin subfamily and has been described in platelets, endothelial cells, melanoma, smooth muscle cells and on the surface of osteoclasts (Horton and Davies, J. Bone Min. Res. 1989, 4:803-808; Davies et al., J. Cell. Biol. 1989, 109:1817-1826; Horton, Int. J. Exp. Pathol., 1990, 71:741-759). Like GPIIb/IIIa, the vitronectin receptor binds a variety of RGD-containing adhesive proteins such as vitronectin, fibronectin, VWF, fibrinogen, osteopontin, bone sialo protein II and thrombospondin in a manner mediated by the RGD sequence. Possible roles for α_v/β_3 in angiogenesis, tumor progression, and neovascularization have been proposed (Brooks et al., Science, 1994, 264:569-571). A key event in bone resorption is the adhesion of osteoclasts to the matrix of bone. Studies with monoclonal antibodies have implicated the α_v/β_3 receptor in this process and suggest that a selective α_v/β_3 antagonist would have utility in blocking bone resorption (Horton et al., J. Bone Miner. Res., 1993, 8:239-247; Helfrich et al., J. Bone Miner. Res., 1992, 7:335-343).

Several RGD-peptidomimetic compounds have been reported which block fibrinogen binding and prevent the formation of platelet thrombi.

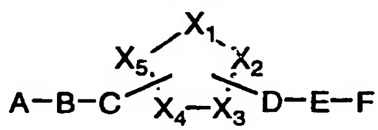
European Patent Application Publication Number 478363 relates to compounds having the general formula:



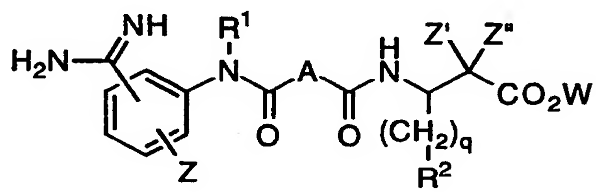
European Patent Application Publication Number 478328 relates to compounds having the general formula:



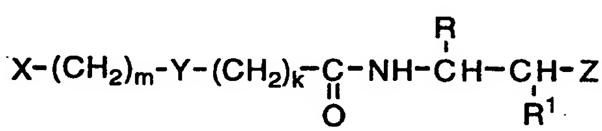
European Patent Application Publication Number 525629 (corresponds to Canadian Patent Application Publication Number 2,074,685) discloses compounds having the general formula:



PCT Patent Application 9307867 relates to compounds having the general formula:



European Patent Application Publication Number 4512831 relates to compounds having the general formula:



None of the above references teaches or suggests the compounds of the present invention which are described in detail below.

Most peptides and peptidomimetics exhibit very low oral bioavailability due to poor absorption and/or

degradation in the GI tract and liver. Therefore, their use is limited to the parenteral route of administration.

Drugs with low bioavailability often have a large variability in pharmacological response due to an associated variability in drug delivery. This large variability in drug delivery may occur when the bioavailability is low because under those conditions, it takes only a small variation in bioavailability to give a large change in plasma drug concentration (W. K. Sietsema, The Absolute Oral Bioavailability of Selected Drug, International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 27 No. 4 - 1989 (179-211)).

Peptides and peptidomimetics have also generally shown relatively low nasal bioavailability. For example, studies with the luteinizing hormone releasing hormone (LHRH) analog, nafarelin acetate, showed that nasal bioavailability was only ~ 2% (S. T. Anik, G. McRae, C. Nerenberg, A. Worden, J. Foreman, J. Hwang, S. Kushinsky, R. E. Jones, and B. Vickery; J. Pharm., Sci. 73: 684-685 (1984)). Thus, the intranasal administration of peptides and peptidomimetics is generally not recommended.

SUMMARY OF THE INVENTION

The present invention provides novel nonpeptide compounds which bind to integrin receptors thereby altering cell-matrix and cell-cell adhesion processes. The compounds of the present invention are useful for the treatment of inflammation, bone degradation, tumors, metastases, thrombosis, and cell aggregation-related conditions in a mammal.

One aspect of this invention provides novel compounds of Formula I (described below) which are useful as antagonists of the platelet glycoprotein IIb/IIIa complex. The compounds of the present invention inhibit the binding of fibrinogen to platelet glycoprotein IIb/IIIa complex and inhibit the aggregation of platelets. The present

invention also includes pharmaceutical compositions containing such compounds of Formula I, and methods of using such compounds for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

The present invention also includes methods of treating cardiovascular disease, thrombosis or harmful platelet aggregation, reocclusion following thrombolysis, reperfusion injury, or restenosis by administering a compound of Formula I alone or in combination with one or more additional therapeutic agents selected from: anti-coagulants such as warfarin or heparin; anti-platelet agents such as aspirin, piroxicam or ticlopidine; thrombin inhibitors such as boroarginine derivatives, hirudin or argatroban; or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase; or combinations thereof.

The present invention also provides novel compounds, pharmaceutical compositions and methods which may be used in the treatment or prevention of diseases which involve cell adhesion processes, including, but not limited to, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, metastasis, wound healing, diabetic retinopathy, inflammatory bowel disease and other autoimmune diseases.

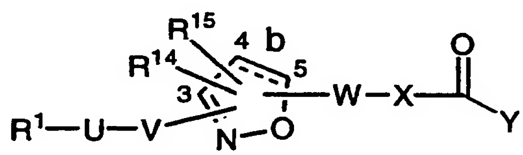
Also included in the present invention are pharmaceutical kits comprising one or more containers containing pharmaceutical dosage units comprising a compound of Formula I, for the treatment of cell adhesion related disorders, including but not limited to thromboembolic disorders.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel nonpeptide compounds of Formula I (described below) which bind to integrin receptors thereby altering cell-matrix and cell-cell adhesion processes. The compounds of the present invention are useful for the treatment of inflammation, bone degradation, tumors, metastases, thrombosis, and cell aggregation-related conditions in a mammal.

One aspect of this invention provides compounds of Formula I (described below) which are useful as antagonists of the platelet glycoprotein IIb/IIIa complex. The compounds of the present invention inhibit the binding of fibrinogen to the platelet glycoprotein IIb/IIIa complex and inhibit the aggregation of platelets. The present invention also includes pharmaceutical compositions containing such compounds of Formula I, and methods of using such compounds for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

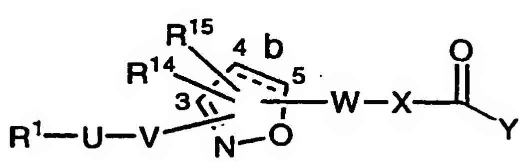
This invention relates to novel compounds of the Formula I:



(I)

or a pharmaceutically acceptable salt or prodrug form thereof.

[1] A first embodiment of this invention provides compounds of Formula I:

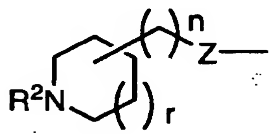


(I)

or pharmaceutically acceptable salt or prodrug forms thereof wherein:

b is a single or double bond;

R^1 is selected from $R^2(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ-$, piperazinyl-$(CH_2)_qZ-$ or



;

Z is selected from O, S, S(=O), or $S(=O)_2$;

R^2 and R^3 are independently selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_6-C_{10} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_6-C_{10} aryloxycarbonyl, aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl;

U is selected from:
- a single bond (i.e., U is not present),
- -(C_1-C_7 alkyl)-,
- -(C_2-C_7 alkenyl)-,
- -(C_2-C_7 alkynyl)-,
- -(aryl)- substituted with 0-3 R^{6a}, or
- -(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:
- a single bond (i.e., V is not present);
- -(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;
- -(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;
- -(C_2-C_7 alkynyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

-(aryl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

-(pyridyl)-, substituted with 0-2 groups independently selected from R^6 or R^7; or

-(pyridazinyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

W is selected from:

a single bond (i.e., W is not present),

-(C_1-C_7 alkyl)-,

-(C_2-C_7 alkenyl)-,

-(C_2-C_7 alkynyl)-, or

$-(C(R^5)_2)_nC(=O)N(R^{5a})-$;

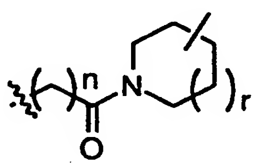
X is selected from:

a single bond (i.e., X is not present);

-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^4, R^8 or R^{14};

-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^4, R^8 or R^{14};

-(C_2-C_7 alkynyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14}; or



;

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-

1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy; or $(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

R^4 and R^{4b} are independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^5 is selected from H, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} can be taken together to be 3-azabicyclononyl, 1-piperidinyl, 1-morpholinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^{5a}$, $SO_2NR^5R^{5a}$, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^{5a}$, $SO_2NR^5R^{5a}$, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, or C_7-C_{11} arylalkyl;

R^8 is selected from:

H;

R^6;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6;

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

C_5-C_6 cycloalkenyl, substituted with 0-2 R^6;

aryl, substituted with 0-2 R^6;

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl(C_1-C_{10} alkoxy)carbonyl;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{15} is selected from:

H;

R^6;

C_1-C_{10} alkyl, substituted with 0-8 R^6;

C_2-C_{10} alkenyl, substituted with 0-6 R^6;

C_1-C_{10} alkoxy, substituted with 0-6 R^6;

aryl, substituted with 0-5 R^6;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;

C_1-C_{10} alkoxycarbonyl substituted with 0-8 R^6;

CO_2R^5; or

$-C(=O)N(R^5)R^{5a}$;

n is 0-4;

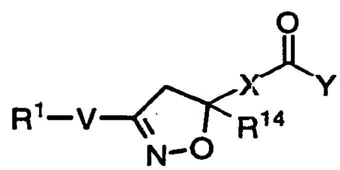
q is 2-7;

r is 0-3;

provided that when b is a double bond, only one of R^{14} or R^{15} is present;

provided that n, q, and r are chosen such that the number of in-chain atoms between R^1 and Y is in the range of 8-18.

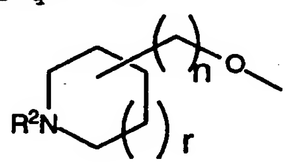
[2] Preferred compounds of this first embodiment are those of Formula II (where W is a single bond (i.e., absent) and U is a single bond (i.e., absent)):



(II)

wherein:

R^1 is selected from $R^2HN(CH_2)_qO$-, $R^2HN(R^2N{=})CNH(CH_2)_qO$-, piperazinyl-$(CH_2)_qO$-, or



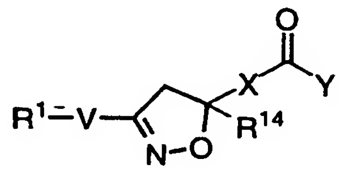
; and/or

R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_{10} alkoxycarbonyl; and/or

R^8 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated; and/or

R^6 and R^7 are selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo.

[3] Further preferred compounds of this first embodiment are those of Formula II (where W is a bond/absent and U is a bond/absent):



(II)

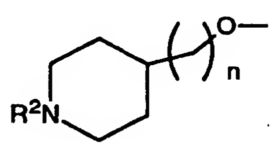
wherein:

X is selected from:
  a single bond (i.e., X is not present);
  -(C_1-C_7 alkyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14};
  -(C_2-C_7 alkenyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14};
  -(C_2-C_7 alkynyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14}; and/or

R^8 is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated.

[4] Further preferred compounds of this first embodiment are compounds of Formula II wherein:

R^1 is



;

V is phenylene or pyridylene;

n is 1 or 2;

X is -(C_1-C_2)alkyl- substituted with 0-2 R^4

Y is selected from:
  hydroxy;
  C_1 to C_{10} alkoxy;
  methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^4 is $-NR^{12}R^{13}$;

R^{12} is H, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, benzyl, benzoyl, phenoxycarbonyl, benzyloxycarbonyl, arylalkylsulfonyl, pyridylcarbonyl, or pyridylmethylcarbonyl; and

R^{13} is H.

[5] Specifically preferred compounds of this first embodiment are compounds, or pharmaceutically acceptable salt or prodrug forms thereof, selected from:

5(*R,S*)-3-[[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl]acetic acid;

5(*R,S*)-*N*-(butanesulfonyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5(*R,S*)-*N*-(*α*-toluenesulfonyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5(*R,S*)-*N*-[(benzyloxy)carbonyl]-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5(*R,S*)-*N*-(pentanoyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;

5(*R,S*)-3-{[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

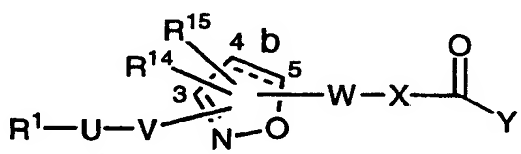
2(*R,S*)-5(*R,S*)-*N*-(butanesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2(*R,S*)-5(*R,S*)-*N*-(α-toluenesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2(*R,S*)-5(*R,S*)-*N*-[(benzyloxy)carbonyl]amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2(*R,S*)-5(*R,S*)-*N*-(pentanoyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid.

[6] A second embodiment of this invention provides a compound of Formula I:

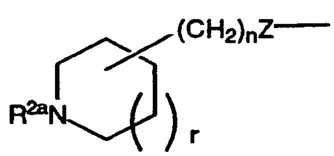


(I)

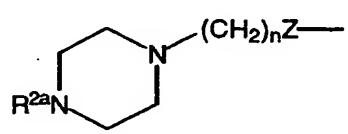
or a pharmaceutically acceptable salt or prodrug form thereof wherein:

b is a single or double bond;

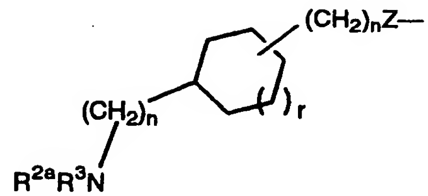
R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N=)C-$, $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, or $R^2(R^3)N(R^5ON=)C-$;



,



or



;

Z is selected from a bond (i.e. is absent), O, S, S(=O), $S(=O)_2$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups

selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

R^{2a} is R^2 or $R^2(R^3)N(R^2N=)C-$;

U is selected from:

a single bond (i.e., U is not present),

-(C_1-C_7 alkyl)-,

-(C_2-C_7 alkenyl)-,

-(C_2-C_7 alkynyl)-,

-(aryl)- substituted with 0-3 R^{6a}, or

-(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:

a single bond (i.e., V is not present);

-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkynyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^6 or R^7;

-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^6 or R^7; or

-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^6 or R^7,

Q is selected from:
a single bond (i.e., Q is not present),
$-O-$, $-S(O)_m-$, $-N(R^{12})-$, $-(CH_2)_m-$, $-C(=O)-$,
$-N(R^{5a})C(=O)-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $-OCH_2-$,
$-CH_2N(R^{12})-$, $-N(R^{12})CH_2-$, $-CH_2C(=O)-$, $-C(=O)CH_2-$,
$-CH_2S(O)_m-$, or $-S(O)_mCH_2-$,

provided that when b is a single bond, and R^1-U-V- is a substituent on C5 of the central 5-membered ring of Formula I, then Q is not $-O-$, $-S(O)_m-$, $-N(R^{12})-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $CH_2N(R^{12})-$ or $-CH_2S(O)_m-$;

W is selected from:
$-(C(R^4)_2)_nC(=O)N(R^{5a})-$, or
$-C(=O)-N(R^{5a})-(C(R^4)_2)_n-$;

X is selected from:
a single bond (i.e. X is absent) -
$-(C(R^4)_2)_n-C(R^4)(R^8)-C(R^4)(R^{4a})-$, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl;

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, $(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

alternately, two R^4 groups on adjacent carbons may join to form a bond (i.e. a carbon-carbon double or triple bond);

R^{4a} is selected from H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, heteroaryl substituted with 0-3 R^6 or C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_7-C_{14} bicycloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{12})R^{13}$; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

R^5 is selected from H, C_1-C_8 alkyl, C_3-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3-C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} when both are substituents on the same nitrogen atom (as in $-NR^5R^{5a}$) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-

piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_mR^{5a}$, $SO_2NR^5R^{5a}$, $SiMe_3$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, -N(R^{12})R^{13}, cyano, halo, CF_3, CHO, CO_2R^5, C(=O)R^{5a}, $CONR^5R^{5a}$, OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR^5R^{5a}, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C$(=O)R^{5a}, $NR^{5a}C$(=O)OR^{5b}, $NR^{5a}C$(=O)NR^5R^{5a}, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, S(O)$_mR^{5a}$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to C_{11} arylalkyl;

R^8 is selected from:

R^6;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6;

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

C_5-C_6 cycloalkenyl, substituted with 0-3 R^6;

aryl, substituted with 0-3 R^6;

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl(C_2-C_{10} alkenyl)sulfonyl, heteroarylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_7-C_{11} arylcarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{15} is selected from:

H; R^6; $-CO_2R^5$; $-C(=O)N(R^5)R^{5a}$;

C_1-C_{10} alkoxycarbonyl substituted with 0-2 R^6;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_1-C_{10} alkoxy, substituted with 0-3 R^6;

aryl, substituted with 0-3 R^6; or

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

provided that when b is a double bond, only one of R^{14} or R^{15} is present;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-C(=O)N(R^{18b})_2$,

$-C(=O)NHSO_2R^{18a}$,

$-C(=O)NHC(=O)R^{18b}$,

$-C(=O)NHC(=O)OR^{18a}$,

$-C(=O)NHSO_2NHR^{18b}$,

$-C(=S)-NH-R^{18b}$,

$-NH-C(=O)-O-R^{18a}$,

$-NH-C(=O)-R^{18b}$,

$-NH-C(=O)-NH-R^{18b}$,

$-SO_2-O-R^{18a}$,

$-SO_2-R^{18a}$,

$-SO_2-N(18^b)_2$,

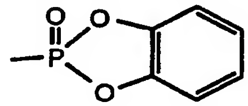
$-SO_2-NHC(=O)O18^b$,

$-P(=S)(OR^{18a})_2$,

$-P(=O)(OR^{18a})_2$,

$-P(=S)(R^{18a})_2$,

$-P(=O)(R^{18a})_2$, or



;

R^{17} is selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-;

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},

C_2-C_8 alkenyl substituted with 0-2 R^{19},

C_2-C_8 alkynyl substituted with 0-2 R^{19},

C_3-C_8 cycloalkyl substituted with 0-2 R^{19},

aryl substituted with 0-4 R^{19},

aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19},

C_1-C_6 alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

m is 0-2;

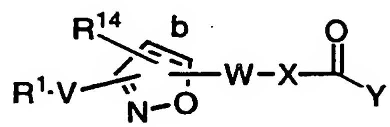
n is 0-4;

q is 1-7;

r is 0-3;

provided that n, q and r are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-18.

[7] Preferred compounds of this second embodiment are those compounds of Formula Ia:



(Ia)

wherein:

Z is selected from a bond (i.e. is absent), O, or S; and/or

R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, or C_1-C_{10} alkoxycarbonyl; and/or

W is $-(CH_2)_nC(=O)N(R^{5a})-$; and/or

X is $-(C(R^4)_2)_n-C(R^4)(R^8)-CH(R^4)-$, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl; and/or

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b}; and/or

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, $-NR^5R^{5a}$, CO_2R^5, $S(O)_mR^5$, OR^5, cyano, halo;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

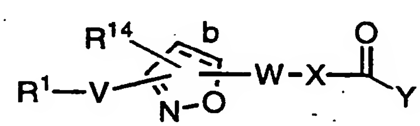
a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7; and/or

R^7 is selected from selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo; and/or

R^8 is selected from:
$-CONR^5NR^{5a}$; $-CO_2R^5$;
C_1-C_{10} alkyl, substituted with 0-3 R^6;
C_2-C_{10} alkenyl, substituted with 0-3 R^6;
C_2-C_{10} alkynyl, substituted with 0-3 R^6,
C_3-C_8 cycloalkyl, substituted with 0-3 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-3 R^6;
aryl, substituted with 0-2 R^6;
5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6; and/or

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylcarbonyl, or heteroarylalkylcarbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2.

[8] Further preferred compounds of this second embodiment are those compounds of Formula Ia:



(Ia)

wherein:

Z is selected from a bond (i.e. is absent) or O; and/or

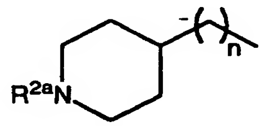
W is $-(CH_2)_nC(=O)N(R^{12})-$; and/or

X is $-C(R^4)(R^8)-C(R^4)_2-$.

[9] Further preferred compounds of this second embodiment are compounds of Formula Ia, wherein:

R^1 is $R^2NHC(=NR^2)-$, $R^2NHC(=NR^2)NH-$ and V is phenylene or pyridylene, or

R^1 is



and V is a single bond (i.e. V is absent);

n is 1 or 2;

X is $-CHR^8CH_2-$;

Y is selected from:

hydroxy;

C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

1-(i-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(*t*-butyloxycarbonyloxy)ethoxy-;

dimethylaminoethoxy-;

diethylaminoethoxy-;

(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;

1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^6 is selected from H, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, $-NR^5R^{5a}$, CO_2R^5, $S(O)_mR^5$, OR^5, cyano, halo;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl;

R^8 is selected from:

$-CONR^5NR^{5a}$; $-CO_2R^5$;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6,

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

aryl, substituted with 0-2 R^6;

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} is selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylsulfonyl,

aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, aryl, pyridylcarbonyl or pyridylmethylcarbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2; and

R^{13} is H.

[10], [35] Specifically preferred compounds of this second embodiment are compounds, or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt or prodrug forms thereof, selected from:

3(*R,S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoic acid;

3(*R,S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-pentanoic acid;

3(*R*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}heptanoic acid;

3(*R,S*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylthio)butanoic acid;

3(*R,S*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylsulfonamido)butanoic acid;

3(*R,S*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(*n*-butylsulfonamido)butanoic acid;

3(*S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(adamantylmethylaminocarbonyl)propanoic acid;

3(*S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(1-azabicyclo[3.2.2]nonylcarbonyl)propanoic acid;

3(*S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(phenethylaminocarbonyl)propanoic acid;

3(*R*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(3-pyridylethyl)propanoic acid;

3(*R*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(2-pyridylethyl)propanoic acid;

3(*R*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(phenylpropyl)propanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(phenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methyl-phenyl-sulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(butanesulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(propanesulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(ethanesulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(ethyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(1-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(1-(2-methyl)-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(2-methyl)-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(benzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methylbenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methoxybenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-chlorobenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-bromobenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-fluorobenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-phenoxybenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(methyloxyethyl)-oxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-pyridinylcarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-pyridinylcarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-pyridinyl-carbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(2-pyridinyl)-acetyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(3-pyridinyl)-acetyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(4-pyridinyl)-acetyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-pyridyl-methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-pyridyl-methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-pyridyl-methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-butyloxyphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-thienylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-iodophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-trifluoromethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-chlorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-2-methoxycarbonylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2,4,6-trimethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-chlorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-trifluoromethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-trifluoromethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-fluorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-fluorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methoxyphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2,3,5,6-tetramethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-cyanophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-chlorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-propylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-phenylethylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-isopropylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-phenylpropylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-pyridylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(phenylaminosulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(benzylaminosulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(dimethylaminosulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(phenylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-fluorophenylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(1-naphthylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(benzylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-bromo-2-thienylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methyl-2-benzothienylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-cyclopropylethoxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{5-(4-formamidinophenyl)-isoxazolin-3-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-methyl-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

said enantiomeric and diasteriomeric forms being selected from:

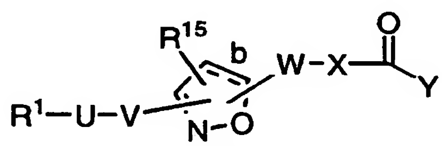
(*R*,*S*), (*R*,*S*);
(*R*), (*R*,*S*);
(*S*), (*R*,*S*);
(*R*), (*R*);
(*S*), (*R*);
(*R*), (*S*);
(*S*), (*S*).

The prodrug forms of the compounds of the second embodiment include the following esters:

methyl;
ethyl;
isopropyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;

1-(ethylcarbonyloxy)ethyl-;
1-(t-butylcarbonyloxy)ethyl-;
1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxycarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
t-butyloxycarbonyloxymethyl-;
1-(i-propyloxycarbonyloxy)ethyl-;
1-(cyclohexyloxycarbonyloxy)ethyl-;
1-(t-butyloxycarbonyloxy)ethyl-;
dimethylaminoethyl-;
diethylaminoethyl-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;
1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

[11] Also preferred compounds of the second embodiment are those compounds of Formula Ic:

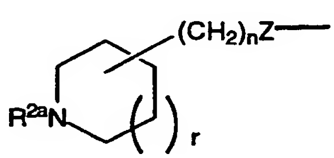


(Ic)

wherein:

b is a single or double bond;

R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N=)C-$, $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, or $R^2(R^3)N(R^5ON=)C-$;



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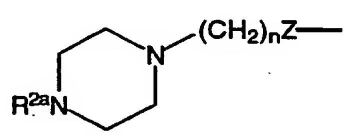

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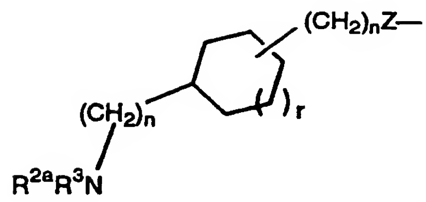


;

Z is selected from a bond (i.e. is absent), O, or S;

R^2 and R^3 are independently selected from: H; C_1-C_6 alkyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

R^{2a} is R^2 or $R^2(R^3)N(R^2N=)C$;

U is a single bond (i.e., U is not present),

V is selected from:

a single bond (i.e., V is not present);

-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkynyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^6 or R^7;

-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^6 or R^7; or

-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^6 or R^7,

Q is selected from
a single bond (i.e., Q is not present),
$-O-$, $-S(O)_m-$, $-N(R^{12})-$, $-(CH_2)_m-$, $-C(=O)-$, $-N(R^{5a})C(=O)-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $-OCH_2-$, $-CH_2N(R^{12})-$, $-N(R^{12})CH_2-$, $-CH_2C(=O)-$, $-C(=O)CH_2-$, $-CH_2S(O)_m-$, or $-S(O)_mCH_2-$,

provided that when b is a single bond, and R^1-U-V- is a substituent on C5 of the central 5-membered ring in Formula I, then Q is not $-O-$, $-S(O)_m-$, $-N(R^{12})-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $CH_2N(R^{12})-$ or $-CH_2S(O)_m-$;

W is selected from:
$-(C(R^4)_2)-C(=O)-N(R^{5a})-$, or
$-C(=O)-N(R^{5a})-(C(R^4)_2)-$;

X is $-C(R^4)_2-CHR^{4a}-$;

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{4a} is selected from hydroxy, C_1-C_{10} alkoxy, nitro, $-N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, or $-N(R^{16})R^{17}$,
C_1-C_{10} alkyl substituted with 0-3 R^6,
aryl substituted with 0-3 R^6,
heteroaryl substituted with 0-3 R^6, or
C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{12})R^{13}$, halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridyl;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11}

cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, or adamantylmethyl, C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} can be taken together to be 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl or C_7-C_{11} arylalkoxycarbonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b}

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, -N(R^{12})R^{13}, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl,

C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{15} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,
$-C(=O)-R^{18b}$,
$-C(=O)N(R^{18b})_2$,
$-SO_2-R^{18a}$, or
$-SO_2-N(R^{18b})_2$;

R^{17} is selected from: H or C_1-C_4 alkyl;

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl,

thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C2-C6 alkynyl, C_1-C_6 alkoxy, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, heteroaryl, aryl(C_1-C_6 alkyl)-, or C_1-C_4 alkoxycarbonyl;

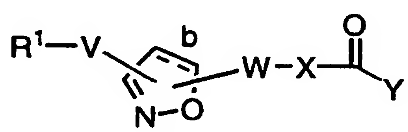
n is 0-4;

q is 1-7;

r is 0-3;

provided that n, q, and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

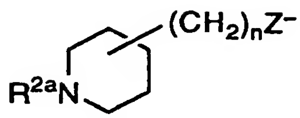
[12] Further preferred compounds of the second embodiment of Formula Ic are those compounds of Formula Ib:



(Ib)

wherein:

R^1 is selected from: $R^2(R^3)N$-, $R^2NH(R^2N{=})C$-, $R^2NH(R^2N{=})CNH$-, $R^2R^3N(CH_2)_{p'}Z$-, $R^2NH(R^2N{=})CNH(CH_2)_{p'}Z$-, $R^2(R^3)NC(O)$-, $R^2(R^5O)N(R^2N{=})C$-, or $R^2(R^3)N(R^5ON{=})C$-;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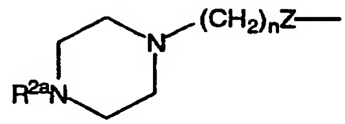
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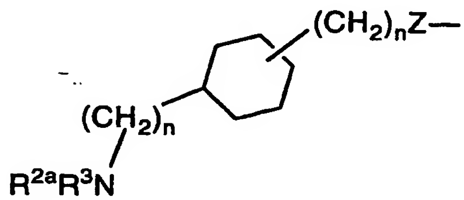

;

n is 0-1;

p' is 4-6;

p" is 2-4;

Z is selected from a bond (i.e. is absent) or O;

V is a single bond (i.e., V is not present), -(phenyl)- or -(pyridyl)-;

W is selected from:

$-(C(R^4)_2)-C(=O)-N(R^{5a})-$,

$-C(=O)-N(R^{5a})-CH_2-$;

X is selected from:

$-CH_2-CHN(R^{16})R^{17}-$, or

$-CH_2-CHNR^5R^{5a}-$;

Y is selected from:

hydroxy;

C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;

t-butyloxycarbonyloxymethoxy-;

1-(i-propyloxycarbonyloxy)ethoxy-;

1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{16} is selected from:
$-C(=O)-O-R^{18a}$,
$-C(=O)-R^{18b}$,
$-S(=O)_2-R^{18a}$ or
$-SO_2-N(R^{18b})_2$;

R^{17} is selected from H or C_1-C_5 alkyl;

R^{18a} is selected from:
C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

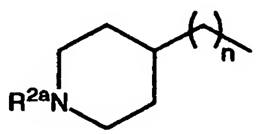
C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl,

piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19}.

[13] Further preferred compounds of Formula Ib are those compounds wherein:

R^1 is $R^2NH(R^2N=)C-$ or $R^2HN(R^2N=)CNH-$ and V is phenylene or pyridylene; or

R^1 is



and V is a single bond (i.e. V is absent);

n is 1 or 2;

R^{18a} is selected from:

C_1-C_4 alkyl substituted with 0-2 R^{19},

C_2-C_4 alkenyl substituted with 0-2 R^{19},

C_2-C_4 alkynyl substituted with 0-2 R^{19},

C_3-C_7 cycloalkyl substituted with 0-2 R^{19},

aryl substituted with 0-4 R^{19},

aryl(C_1-C_4 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_4 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl,

isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19}.

[14] Specifically preferred compounds of Formula Ib are compounds, or pharmaceutically acceptable salt forms thereof, selected from:

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(phenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methyl-phenyl-sulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(butanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(propanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(ethanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(ethyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(1-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(1-(2-methyl)-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(2-methyl)-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methylbenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methoxybenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-chlorobenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-bromobenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-fluorobenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-phenoxybenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(methyloxyethyl)-oxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-pyridinylcarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-pyridinylcarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-pyridinyl-carbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(2-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(3-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(4-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-butyloxyphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-thienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R,S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-iodophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-2-methoxycarbonylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2,4,6-trimethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-fluorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-fluorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methoxyphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2,3,5,6-tetramethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-cyanophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-propylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-phenylethylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-isopropylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-phenylpropylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-pyridylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(phenylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(benzylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(dimethylaminosulfonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(phenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-fluorophenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(1-naphthylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(benzylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-bromo-2-thienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methyl-2-benzothienylsulfonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid, and

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid.

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid.

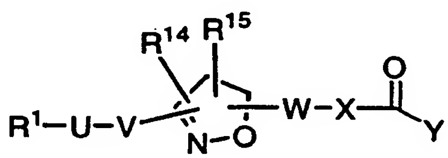
N^3-[2-{5-(4-formamidinophenyl)-isoxazolin-3(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

[15] Also specifically preferred are prodrug esters of the specifically preferred compounds of Formula Ib, said esters being chosen from the group consisting of:

methyl;
ethyl;
isopropyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;

1-(ethylcarbonyloxy)ethyl-;
1-(t-butylcarbonyloxy)ethyl-;
1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxycarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
t-butyloxycarbonyloxymethyl-;
1-(i-propyloxycarbonyloxy)ethyl-;
1-(cyclohexyloxycarbonyloxy)ethyl-;
1-(t-butyloxycarbonyloxy)ethyl-;
dimethylaminoethyl-;
diethylaminoethyl-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;
1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

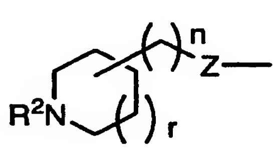
[16] A third embodiment of this invention provides a compound of Formula Id:

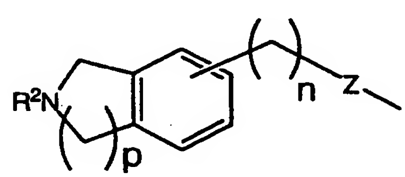


(Id)

or a pharmaceutically acceptable salt or prodrug form thereof wherein:

R^1 is selected from is selected from $R^2(R^3)N$-, $R^2(R^3)N(R^2N{=})C$-, $R^2(R^3)N(R^2N{=})CN(R^2)$-, $R^2(R^3)N(CH_2)_qZ$-, $R^2(R^3)N(R^2N{=})C(CH_2)_qZ$-, $R^2(R^3)N(R^2N{=})CN(R^2)(CH_2)_qZ$-, piperazinyl-$(CH_2)_qZ$-, $R^2(R^3)NC(O)$-, $R^2(R^5O)N(R^2N{=})C$-, $R^2(R^3)N(R^5ON{=})C$-,



, or


;

Z is selected from a bond (i.e., is absent), O, S, S(=O), or $S(=O)_2$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; , C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl;

heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

U is selected from:
a single bond (i.e., U is absent)
C_1-C_7 alkylene,
C_2-C_7 alkenylene,
C_2-C_7 alkynylene,
arylene substituted with 0-3 R^{6a},, or
pyridylene substituted with 0-3 R^{6a};

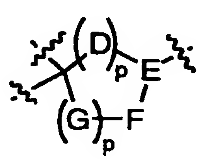
V is selected from:
a single bond (i.e., V is absent);
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-4 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

X is selected from:
a single bond (i.e., X is absent);
$-(CH_2)_nC(=O)N(R^{12})-$;
C_1-C_7 alkylene substituted with 0-6 R^4, R^8 or R^{15};
C_2-C_7 alkenylene substituted with 0-4 R^4, R^8 or R^{15};
C_2-C_7 alkynylene substituted with 0-4 R^4, R^8 or R^{15};

Y is selected from:
hydroxy,
C_1 to C_{10} alkyloxy,
C_3 to C_{11} cycloalkyloxy,
C_6 to C_{10} aryloxy,

C_7 to C_{11} aralkyloxy,
C_3 to C_{10} alkylcarbonyloxyalkyloxy,
C_3 to C_{10} alkoxycarbonyloxyalkyloxy,
C_2 to C_{10} alkoxycarbonylalkyloxy,
C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonylalkyloxy,
C_7 to C_{11} aryloxycarbonylalkyloxy,
C_8 to C_{12} aryloxycarbonyloxyalkyloxy,
C_8 to C_{12} arylcarbonyloxyalkyloxy,
C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy,
C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;
$(R^2)(R^3)N-(C_1-C_{10}$ alkoxy$)-$;

R^{14} and W are attached to the same carbon and taken together to form a spiro-fused, 5-7 membered ring structure of the formula:


;

D, E, F and G are each independently selected from:
$C(R^{6a})_2$;
carbonyl;
a heteroatom moiety selected from N, $N(R^{12})$, O, provided that no more than 2 of D, E, F and G are N, $N(R^{12})$, O, S, or C(=O);
alternatively, the bond between D and E, E and F, or F and G in such spiro-fused ring may be a carbon-nitrogen double bond or a carbon-carbon double bond;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^{5a}, $C(=O)R^{5a}$, $CONHR^{5a}$, $CON(R^{12})_2$, $OC(=O)R^{5a}$, $OC(=O)OR^{5a}$, OR^{5a}, $OC(=O)N(R^{12})_2$, $OCH_2CO_2R^{5a}$, $CO_2CH_2CO_2R^{5a}$, $N(R^{12})_2$, NO_2, $NR^{12}C(=O)R^{5a}$, $NR^{12}C(=O)OR^{5a}$, $NR^{12}C(=O)N(R^{12})_2$, $NR^{12}SO_2N(R^{12})_2$, $NR^{12}SO_2R^{5a}$, $S(O)_pR^{5a}$, $SO_2N(R^{12})_2$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^8 is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_2-C_{10} alkynyl, substituted with 0-6 R^6;
C_3-C_8 cycloalkyl, substituted with 0-6 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-5 R^6;
aryl, substituted with 0-5 R^6;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryls or heteroaryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^5 and R^{5a} are selected independently from H, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, C_7 to C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-8 R^4;

R^{15} is selected from:

H;

R^6;

C_1-C_{10} alkyl, substituted with 0-8 R^6;

C_2-C_{10} alkenyl, substituted with 0-6 R^6;

C_1-C_{10} alkoxy, substituted with 0-6 R^6;

aryl, substituted with 0-5 R^6;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully

unsaturated, said heterocyclic ring being substituted with 0-5 R^6;

C_1-C_{10} alkoxycarbonyl substituted with 0-8 R^6;

CO_2R^5; or

$-C(=O)N(R^{12})R^{13}$;

n is 0-4;

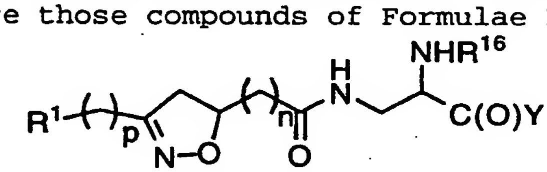
p is 1-3;

q is 1-7;

r is 0-3;

provided that n, p, q and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

[47] Also preferred compounds of the second embodiment are those compounds of Formulae Ie or If:



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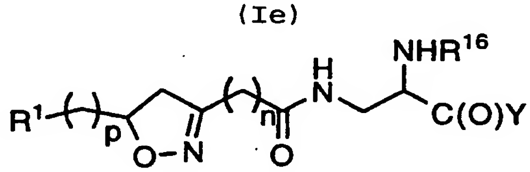


(If)

or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt form thereof, wherein:

R^1 is $R^2(R^3)N(R^2N=)C-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, or $R^2(R^3)N-$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_7-

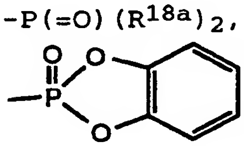
C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl(C_2-C_{10} alkenyl)sulfonyl, heteroarylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_7-C_{11} arylcarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{16} is selected from:

-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-C(=O)N(R^{18b})$_2$,
-C(=O)NHSO$_2$$R^{18a}$,
-C(=O)NHC(=O)R^{18b},
-C(=O)NHC(=O)OR^{18a},
-C(=O)NHSO$_2$NHR^{18b},
-C(=S)-NH-R^{18b},
-NH-C(=O)-O-R^{18a},
-NH-C(=O)-R^{18b},
-NH-C(=O)-NH-R^{18b},
-SO$_2$-O-R^{18a},
-SO$_2$-R^{18a},
-SO$_2$-N(18^b)$_2$,
-SO$_2$-NHC(=O)O18^b,
-P(=S)(OR^{18a})$_2$,
-P(=O)(OR^{18a})$_2$,
-P(=S)(R^{18a})$_2$,
-P(=O)(R^{18a})$_2$, or


;

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19},

C_1-C_6 alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19};

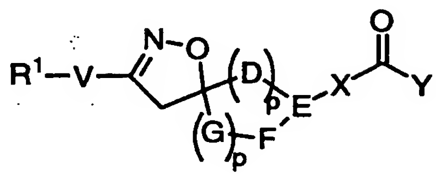
R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, $(R^2)(R^3)N$-(C_1-C_{10} alkoxy)-;

m is 0-2;
n is 0-2; and
p is 1-5.

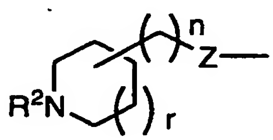
[17] Preferred compounds of this third embodiment are compounds of Formula III:



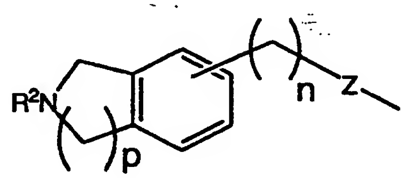
(III)

wherein:

R^1 is selected from R^2HN-, $H_2N(R^2N=)C$-, $H_2N(R^2N=)CNH$-, $R^2HN(CH_2)_qO$-, $H_2N(R^2N=)CNH(CH_2)_qO$-, piperazinyl-$(CH_2)_qO$-, $R^2(R^3)NC(O)$-, $R^2(R^5O)N(R^2N=)C$-, $R^2(R^3)N(R^5ON=)C$-,



, or



;

R^2 and R^3 are selected from H; C_1-C_6 alkyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl,

methylenedioxydiyl, ethylenedioxydiyl; or C_1-C_{10} alkoxycarbonyl;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

V is selected from:
a single bond (i.e., V is absent);
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-3 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

X is selected from $-(CH_2)_nC(=O)N(R^{12})-$, C_1-C_7 alkylene substituted with 0-1 R^4, C_2-C_7 alkenylene, or C_2-C_7 alkynylene;

Y is selected from:
hydroxy,
C_1 to C_{10} alkyloxy,
C_3 to C_{11} cycloalkyloxy,
C_6 to C_{10} aryloxy,
C_7 to C_{11} aralkyloxy,
C_3 to C_{10} alkylcarbonyloxyalkyloxy,
C_3 to C_{10} alkoxycarbonyloxyalkyloxy,
C_2 to C_{10} alkoxycarbonylalkyloxy,
C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonylalkyloxy,
C_7 to C_{11} aryloxycarbonylalkyloxy,
C_8 to C_{12} aryloxycarbonyloxyalkyloxy,
C_8 to C_{12} arylcarbonyloxyalkyloxy,
C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy,
C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or
C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

Z is selected from O or CH_2;

D, E, F and G are each independently selected from:

CH_2;

carbonyl;

a heteroatom moiety selected from N, NH, O, provided that no more than 2 of D, E, F and G are N, NH, O or S;

alternatively, the bond between D and E, E and F, or F and G in such spiro-fused ring may be a carbon-nitrogen double bond or a carbon-carbon double bond;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, -N(R^{12})R^{13}, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroaryalkylcarbonyl or aryl;

n is 0-4;

p is 1-3;

q is 1-7;

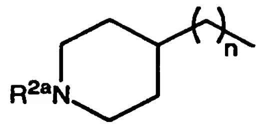
r is 0-3;

provided that n, p, q and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

[18] Further preferred compounds of this third embodiment are compounds of Formula II wherein:

R^1 is R^2NHC(=NR^2)- and V is phenyl or pyridyl or

R^1 is

 and V is a single bond (i.e. V is absent);

n is 1 or 2;

X is C_1-C_4 alkylene substituted with 0-1 R^4;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{12} and R^{13} are each independently selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl,

arylsulfonyl, heteroarylcarbonyl, heteroaryalkylcarbonyl or aryl; and

R^{13} is H.

[19] Specifically preferred compounds of this third embodiment are compounds, or pharmaceutically acceptable salt or prodrug forms thereof, selected from:

5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;
5(*R,S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5,7-dione;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

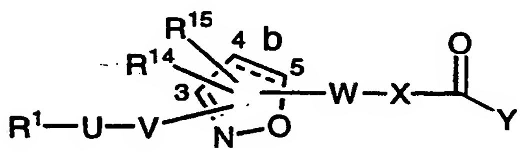
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5(R,S)-3-(4-amidinophenyl)-8-[2-(benzyloxycarbonylamino)-2-carboxyethyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene.

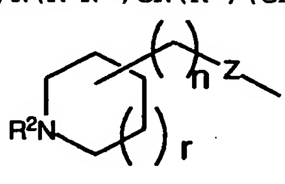
[20] A fourth embodiment of this invention provides compounds of Formula I:



(I)

or pharmaceutically acceptable salt or prodrug forms thereof, wherein:

R^1 is selected from:
$R^2(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ-$, piperazinyl-$(CH_2)_qZ-$ or



;

Z is selected from O, S, S(=O), $S(=O)_2$;

R^2 and R^3 are independently selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7

alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl;

U is optionally present and is selected from C_1-C_7 alkylene, C_2-C_7 alkenylene, C_2-C_7 alkynylene, arylene, or pyridylene;

V is selected from:
a single bond (i.e., V is absent);
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-4 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

W is -(aryl)-Z^1-, wherein said aryl is substituted with 0-6 R^6 or R^7;

Z^1 is selected from a single bond (i.e., Z^1 is absent), -CH_2-, O or S;

X is selected from:
a single bond (i.e., X is absent);
C_1-C_7 alkylene substituted with 0-6 R^4, R^8 or R^{15};
C_2-C_7 alkenylene substituted with 0-4 R^4, R^8 or R^{15};
C_2-C_7 alkynylene substituted with 0-4 R^4, R^8 or R^{15};

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10}

alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy; $(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^{5a}, $C(=O)R^{5a}$, $CONHR^{5a}$, $CON(R^{12})_2$, $OC(=O)R^{5a}$, $OC(=O)OR^{5a}$, OR^{5a}, $OC(=O)N(R^{12})_2$, $OCH_2CO_2R^{5a}$, $CO_2CH_2CO_2R^{5a}$, $N(R^{12})_2$, NO_2, $NR^{12}C(=O)R^{5a}$, $NR^{12}C(=O)OR^{5a}$, $NR^{12}C(=O)N(R^{12})_2$, $NR^{12}SO_2N(R^{12})_2$, $NR^{12}SO_2R^{5a}$, $S(O)_pR^{5a}$, $SO_2N(R^{12})_2$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with halogen, alkoxy, alkyl, $-CF_3$, $S(O)_mMe$, or $-NMe_2$; or

C_7 to C_{11} arylalkyl said aryl being optionally substituted with halogen, alkoxy, alkyl, $-CF_3$, $S(O)_mMe$, or $-NMe_2$;

R^8 is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;

C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_2-C_{10} alkynyl, substituted with 0-6 R^6;
C_3-C_8 cycloalkyl, substituted with 0-6 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-5 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl(C_1-C_{10} alkoxy)carbonyl;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^{12})R^{13}$;

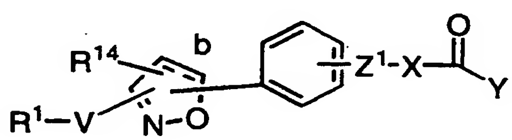
R^5 and R^{5a} are selected independently from H, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, C_7 to C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-8 R^4;

R^{15} is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;

C_1-C_{10} alkoxy, substituted with 0-6 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;
C_1-C_{10} alkoxycarbonyl substituted with 0-8 R^6;
CO_2R^5; or
$-C(=O)N(R^{12})R^{13}$;

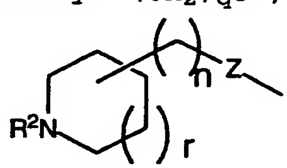
n is 0-4;
q is 2-7;
r is 0-3;
provided that n, q, and r are chosen such that the number of atoms between R^1 and Y is about 8-17.

[21] Preferred compounds of this fourth embodiment are those of Formula IV:



(IV)

wherein:
R^1 is selected from $R^2HN(CH_2)_qO$-, $R^2HN(R^2N{=}C)NH(CH_2)_qO$-, piperazinyl-$(CH_2)_qO$-, or



;

Z is O;

R^2 is selected from H, aryl(C_1-C_{10})alkoxycarbonyl, C_1-C_{10} alkoxycarbonyl;

V is selected from:
a single bond (i.e., V is absent);
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-3 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

Z^1 is selected from a single bond (i.e., Z^1 is absent), O or S;

X is selected from:
a single bond (i.e., X is absent);
C_1-C_7 alkylene substituted with 0-4 R^4, R^8 or R^{15};
C_2-C_7 alkenylene substituted with 0-3 R^4, R^8 or R^{15};
C_2-C_7 alkynylene substituted with 0-3 R^4, R^8 or R^{15};

Y selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^6 and R^7 are selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^8 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S, where said heterocyclic ring may be saturated, partially saturated, or fully unsaturated;

R^{12} and R^{13} are independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl;

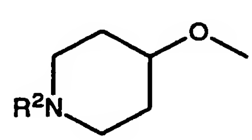
R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^{12})R^{13}$;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^4;

n is 0-4;
q is 2-7;
provided that n and q are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

[22] Further preferred compounds of this fourth embodiment are compounds of Formula IV wherein:

R^1 is $R^2HN(CH_2)_qO$- or



V is C_1-C_3 alkylene;

Z^1 is a single bond (i.e. Z^1 is absent) or O;

X is C_1-C_3 alkylene substituted with 0-1 R^4;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

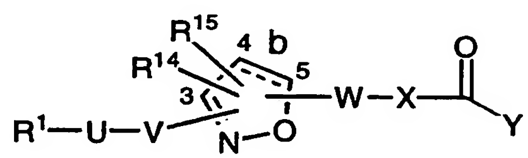
R^{12} and R^{13} are independently selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl;

R^{13} is H.

[23] Specifically preferred compounds of this fourth embodiment are compounds, or pharmaceutically acceptable salt or prodrug forms thereof, selected from:

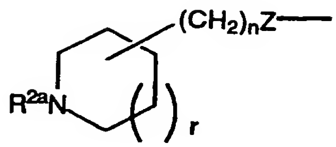
5(*R,S*)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-yl]hydrocinnamic acid;
5(*R,S*)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]hydrocinnamic acid;
5(*R,S*)-4-[3-(3-aminopropyloxymethyl)isoxazolin-5-yl]hydrocinnamic acid;
5(*R,S*)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-yl]phenoxyacetic acid;
5(*R,S*)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]phenoxyacetic acid;
5(*R,S*)-4-[3-(3-aminopropyloxymethyl)isoxazolin-5-yl]phenoxyacetic acid.

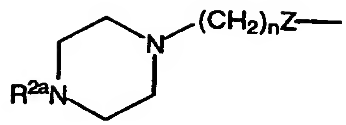
[24] A fifth embodiment of this invention provides a compound of Formula I:



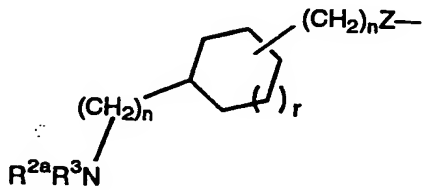
(I)

or a pharmaceutically acceptable salt or prodrug form thereof wherein:
b is a single or double bond;
R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N=)C-$, $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, $R^2(R^3)N(R^5ON=)C-$;





, or



;

Z is selected from a bond (i.e. is absent), O, S, S(=O), $S(=O)_2$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl,

methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

R^{2a} is R^2 or $R^2(R^3)N(R^2N=)C$;

U is selected from:

a single bond (i.e., U is not present),

-(C_1-C_7 alkyl)-,

-(C_2-C_7 alkenyl)-,

-(C_2-C_7 alkynyl)-,

-(aryl)- substituted with 0-3 R^{6a}, or

-(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:

a single bond (i.e., V is not present);

-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

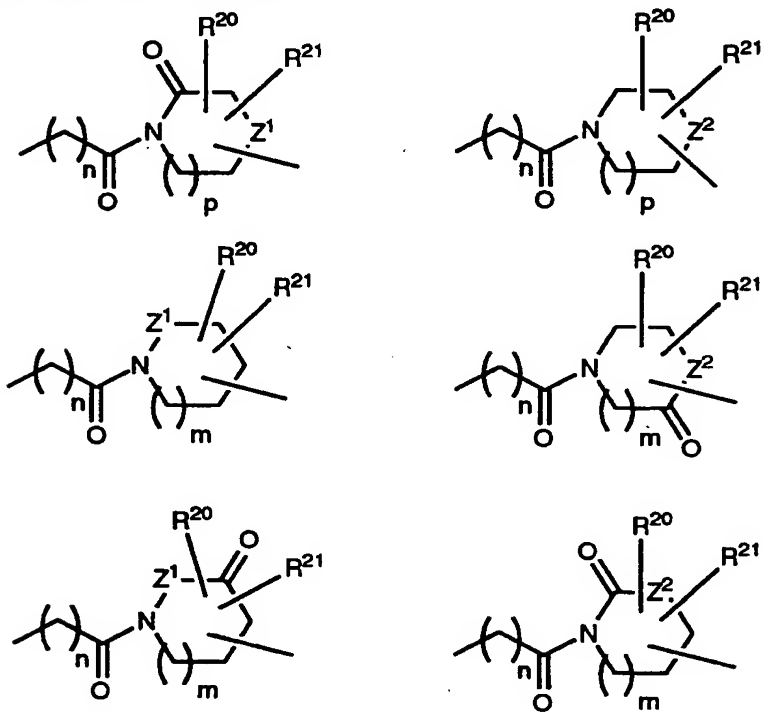
-(C_2-C_7 alkynyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(phenyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

-(pyridyl)-, substituted with 0-2 groups independently selected from R^6 or R^7; or

-(pyridazinyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

W is selected from:



;

X is selected from:

a single bond (i.e. X is absent)

$-(C(R^4)_2)_n-C(R^4)(R^8)-C(R^4)(R^{4a})-$, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl;

Y is selected from:

hydroxy,

C_1 to C_{10} alkyloxy,

C_3 to C_{11} cycloalkyloxy,

C_6 to C_{10} aryloxy,

C_7 to C_{11} aralkyloxy,

C_3 to C_{10} alkylcarbonyloxyalkyloxy,

C_3 to C_{10} alkoxycarbonyloxyalkyloxy,

C_2 to C_{10} alkoxycarbonylalkyloxy,

C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonylalkyloxy,
C_7 to C_{11} aryloxycarbonylalkyloxy,
C_8 to C_{12} aryloxycarbonyloxyalkyloxy,
C_8 to C_{12} arylcarbonyloxyalkyloxy,
C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy,
C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
$(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

Z^1 is -C-, -O-, or $-NR^{22}-$;

Z^2 is -O-, or $-NR^{22}-$;

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkylene cycloalkyl, or cycloalkylalkylene;

alternately, two R^4 groups on adjacent carbons may join to form a bond (i.e. a carbon-carbon double or triple bond);

R^{4a} is selected from H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, or C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{12})R^{13}$; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, or pyridyl;

R^5 is selected from H, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, C_7 to C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} when both are substituents on the same nitrogen atom (as in $-NR^5R^{5a}$) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^5, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^5$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substiuent on aryl; or

a 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_mR^{5a}$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to C_{11} arylalkyl;

R^8 is selected from:

R^6;

C_2-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6;

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

C_5-C_6 cycloalkenyl, substituted with 0-3 R^6;

aryl, substituted with 0-3 R^6;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_7-C_{11} arylcarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{15} is selected from:

H;

R^6;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_1-C_{10} alkoxy, substituted with 0-3 R^6;

aryl, substituted with 0-3 R^6;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

C_1-C_{10} alkoxycarbonyl substituted with 0-2 R^6;

$-CO_2R^5$; or

$-C(=O)N(R^{12})R^{13}$;

provided that when b is a double bond, only one of R^{14} or R^{15} is present;

R^{16} is selected from:

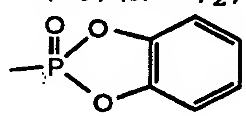
$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-C(=O)N(R^{18b})_2$,

$-C(=O)NHSO_2R^{18a}$,

$-C(=O)NHC(=O)R^{18b}$,
$-C(=O)NHC(=O)OR^{18a}$,
$-C(=O)NHSO_2NHR^{18b}$,
$-C(=S)-NH-R^{18b}$,
$-NH-C(=O)-O-R^{18a}$,
$-NH-C(=O)-R^{18b}$,
$-NH-C(=O)-NH-R^{18b}$,
$-SO_2-O-R^{18a}$,
$-SO_2-R^{18a}$,
$-SO_2-N(18^b)_2$,
$-SO_2-NHC(=O)O18^b$,
$-P(=S)(OR^{18a})_2$,
$-P(=O)(OR^{18a})_2$,
$-P(=S)(R^{18a})_2$,
$-P(=O)(R^{18a})_2$, or



;

R^{17} is selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-;

R^{18a} is selected from:
C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19},

C_1-C_6 alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms

selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

R^{20} and R^{21} are each independently selected from H, C_1-C_{10} alkyl, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $NR^5C(=O)R^{5a}$, $NR^{12}R^{13}$, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, or C_7-C_{11} arylalkyl;

R^{22} is selected from C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-; $C(=O)R^{5a}$, CO_2R^{5b}, $-C(=O)N(R^5)R^{5a}$, or a bond to X;

m is 0-2;

n is 0-2;

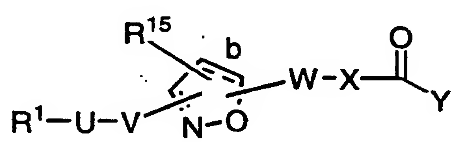
p is 1-2;

q is 1-7;

r is 0-3;

provided that n, q and r are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-17.

[25] Preferred compounds of this embodiment are those compounds of Formula Ic:



(Ic)

wherein:

Z is selected from a bond (i.e. is absent), O, or S;

R^2 and R^3 are independently selected from: H; C_1-C_6 alkyl; C_7-C_{11} arylalkyl optionally substituted with 0-3

groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

U is a single bond (i.e., U is not present);

X is $-CHR^{4a}-$;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b};

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, or aryl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{15} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-S(=O)_2-R^{18a}$;

R^{17} is selected from: H or C_1-C_4 alkyl;

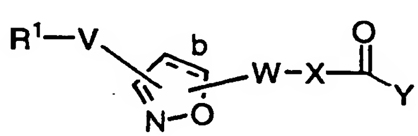
R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-2 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-2 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19}.

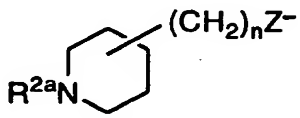
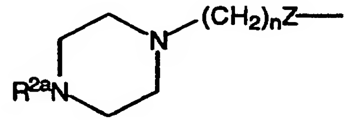
[26] Further preferred compounds of this embodiment are compounds of Formula Ib:



(Ib)

wherein:

R^1 is selected from: $R^2(R^3)N-$, $R^2NH(R^2N=)C-$, $R^2R^3N(CH_2)_{p''}Z-$, $R^2NH(R^2N=)CNH(CH_2)_{p'}Z-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, $R^2(R^3)N(R^5ON=)C-$;


, or

;

n is 0-1;

p' is 2-4;

p" is 4-6;

Z is selected from a bond (i.e. is absent) or O;

R^3 is H or C_1-C_5 alkyl;

V is a single bond (i.e., V is not present), or -(phenyl)-;

X is selected from:
- $-CH_2-$,
- $-CHN(R^{16})R^{17}-$, or
- $-CHNR^5R^{5a}-$;

Y is selected from:

hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;

diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{18a} is selected from:

C_1-C_4 alkyl substituted with 0-2 R^{19},
C_2-C_4 alkenyl substituted with 0-2 R^{19},
C_2-C_4 alkynyl substituted with 0-2 R^{19},
C_3-C_4 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-2 R^{19},
aryl(C_1-C_4 alkyl)- substituted with 0-2 R^{19},

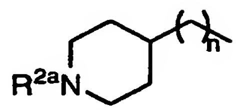
a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19}.

[27] Further preferred compounds of this fifth embodiment are compounds of Formula Ib wherein:

R^1 is $R^2NH(R^2N=)C-$ or $R^2NH(R^2N=)CNH-$ and V is phenyl or pyridyl; or

R^1 is

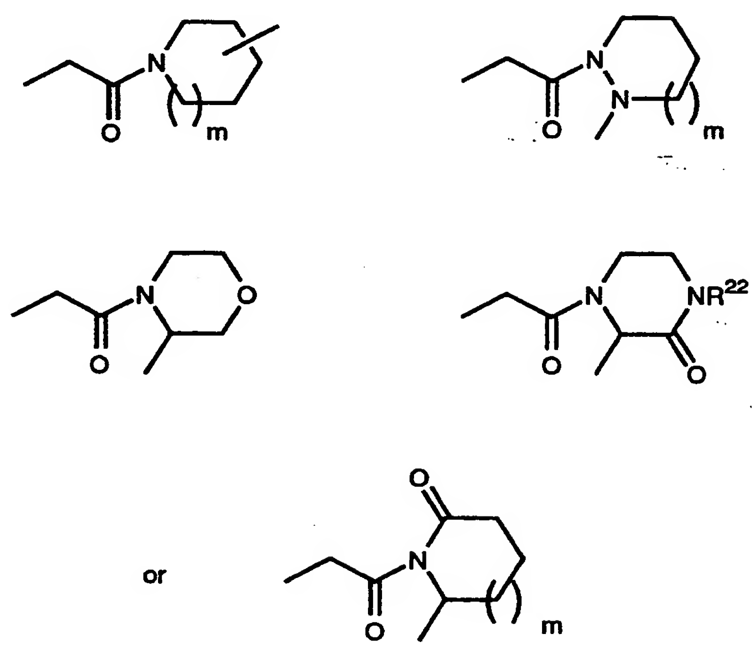


, and V is a single bond (i.e. V is absent)

n is 1-2;

X is selected from:
$-CH_2-$,
$-CHN(R^{16})R^{17}-$, or
$-CHNR^5R^{5a}-$;

W is selected from:



;

m is 1-3;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{19} is H, halogen, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, cyclopropylmethyl, aryl, or benzyl;

R^{20} and R^{21} are both H;

R^{22} is H, C_1-C_4 alkyl or benzyl.

[28] Specifically preferred compounds of this fifth embodiment are compounds of Formula Ib, or pharmaceutically acceptable salt forms thereof, selected from:

2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperidine;
2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azepine;

2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine;

3-(R,S)-carboxymethyl-4-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperazine-2-one;

6-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperidine-2-one;

5-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine-2-one;

7-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azetidine-2-one;

2-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrazolidine;

3-(R,S)-carboxymethyl-4-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]morpholine.

In the present invention it has been discovered that the compounds of Formula I above are useful as inhibitors of cell-matrix and cell-cell adhesion processes. The present invention includes novel compounds of Formula I and methods for using such compounds for the prevention or treatment of diseases resulting from abnormal cell adhesion to the extracellular matrix which comprises administering to a host in need of such treatment a therapeutically effective amount of such compound of Formula I.

In the present invention it has also been discovered that the compounds of Formula I above are useful as inhibitors of glycoprotein IIb/IIIa (GPIIb/IIIa). The compounds of the present invention inhibit the activation and aggregation of platelets induced by all known endogenous platelet agonists.

The present invention also provides pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier.

The compounds of Formula I of the present invention are useful for the treatment (including prevention) of thromboembolic disorders. The term "thromboembolic disorders" as used herein includes conditions involving platelet activation and aggregation, such as arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, thrombosis, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, myocardial infarction, cerebral embolism, kidney embolisms, pulmonary embolisms, or such disorders associated with diabetes, comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Formula I described above.

The compounds of Formula I of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, infammation, bone degradation, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation rejection, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, tumors, metastasis, diabetic retinopathy, inflammatory bowel disease and other autoimmune diseases. The compounds of Formula I of the present invention may also be useful for wound healing.

The compounds of the present invention are useful for inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing

thrombus or embolus formation in a mammal. The compounds of the invention may be used as a medicament for blocking fibrinogen from acting at its receptor site in a mammal.

Compounds of the invention may be administered to patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption, and where the aggregated platelets may form thrombi and thromboemboli. The compounds of the present invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

Extracorporeal circulation is routinely used during cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between GPIIb/IIIa on the platelet membranes and fibrinogen adsorbed to the surface of the extracorporeal circuit. Platelets released from artificial surfaces show impaired homeostatic function. The compounds of the invention may be administered to prevent such *ex vivo* adhesion.

The compounds of the present invention may be used for other *ex vivo* applications to prevent cellular adhesion in biological samples.

Other applications of these compounds include prevention of platelet thrombosis, thromboembolism, and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty of coronary and other arteries and after coronary artery bypass procedures. The compounds of the present invention may also be used to prevent myocardial infarction. The compounds of the

present invention are useful as thrombolytics for the treatment of thromboembolic disorders.

The compounds of the present invention can also be administered in combination with one or more additional therapeutic agents select from: anti-coagulant or coagulation inhibitory agents, such as heparin or warfarin; anti-platelet or platelet inhibitory agents, such as aspirin, piroxicam, or ticlopidine; thrombin inhibitors such as boropeptides, hirudin or argatroban; or thrombolytic or fibrinolytic agents, such as plasminogen activators, anistreplase, urokinase, or streptokinase.

The compounds of Formula I of the present invention can be administered in combination with one or more of the foregoing additional therapeutic agents, thereby to reduce the doses of each drug required to achieve the desired therapeutic effect. Thus, the combination treatment of the present invention permits the use of lower doses of each component, with reduced adverse, toxic effects of each component. A lower dosage minimizes the potential of side effects of the compounds, thereby providing an increased margin of safety relative to the margin of safety for each component when used as a single agent. Such combination therapies may be employed to achieve synergistic or additive therapeutic effects for the treatment of thromboembolic disorders.

By "therapeutically effective amount" it is meant an amount of a compound of Formula I that when administered alone or in combination with an additional therapeutic agent to a cell or mammal is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be

Part E: Methyl 3-(2-*t*-butyloxycarbonylamidinopyrid-5-yl)isoxazolin-5-ylacetate

The part D amidine was BOC protected in standard fashion to afford, after silica gel chromatographic purification, a 41% yield of a colorless foam; HRMS, e/z Calc. for $(M+H)^+$: 363.1668. Found: 363.1682.

Part F: Lithium 3-(2-*t*-butyloxycarbonylamidinopyrid-5-yl)isoxazolin-5-ylacetate

The part E methyl ester (0.37 g, 1.0 mmol) was saponified by stirring with 0.5 M LiOH in MeOH at RT. The MeOH was removed *in vacuo*, then the aqueous mixture was frozen and lyophilized to produce a pale yellow solid quantitatively; HRMS, e/z Calc. for conjugate acid $(M+H)^+$: 349.1512. Found: 349.1531.

Part G: Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(2-amidinopyrid-5-yl)isoxazolin-5-ylacetyl]-*S*-2,3-diaminopropionate hydrochloric acid salt

The part F lithium carboxylate was condensed with methyl N^2-(*m*-toluenesulfonyl)-2,3-diaminopropionate hydrochloride using conditions described above, followed by standard BOC deprotection with 4 M HCl/dioxane to yield a yellow amorphous solid; HRMS, e/z Calc. for $(M+H)^+$: 503.1713. Found: 503.1707.

Example 516A

N^2-(*m*-Toluenesulfonyl)-N^3-[3-(2-amidinopyrid-5-yl)isoxazolin-(*R,S*)-5-ylacetyl]-(*S*)-2,3-diaminopropionic acid trifluoroacetic acid salt.

The methyl ester of Example 516, Part G (31.4 mg, 54.6 nmol) was dissolved in 6M aqueous hydrochloric acid (1 mL) and the mixture was stirred at room temperature for 44 h. The yellow solution was concentrated and subjected to Prep reverse phase HPLC as described in Example 514A,

CH_2Cl_2 (40 mL), and DMF (4 mL) with stirring at ambient temperature. The CH_2Cl_2 was evaporated, and the mixture was diluted with EtOAc, extracted with water (5x) and brine, then dried ($MgSO_4$), filtered, and concentrated. Chromatography on silica gel, eluting with 0% to 70% EtOAc in hexane, afforded 1.4 g of a solid; mp 94-96 °C; HRMS, e/z Calc. for $(M+H)^+$: 255.0536. Found: 255.0531.

Part C: <u>Methyl 3-(2-cyanopyrid-5-yl)isoxazolin-5-ylacetate</u>

The part B chloropyridine (0.51 g, 2.0 mmol), zinc cyanide (0.23 g, 2.0 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), and DMF (2 mL) were heated to 80 °C under N_2 for 3 days. After cooling and concentration, the mixture was preabsorbed onto silica gel by concentration from $CHCl_3$. Chromatography on silica gel, eluting with 0% to 90% EtOAc in hexane afforded 0.28 g of a pale yellow solid; mp 115-116 °C; HRMS, e/z Calc. for $(M+H)^+$: 246.0879. Found: 246.0880. Anal. Calc. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.68; H, 4.48; N, 16.90.

Part D: <u>Methyl 3-(2-amidinopyrid-5-yl)isoxazolin-5-ylacetate formic acid salt</u>

The part C cyanopyridine (0.47 g, 1.9 mmol) and sodium methoxide (prepared *in situ* from Na metal, 4 mg, 0.2 mmol were stirred in dry MeOH (6 mL) at ambient temperature for 16 h, after which ^1H NMR analysis of a reaction aliquot indicated complete formation of methyl imidate [note 9.25 (s, 1H) and 3.92 (s, 3H)]. Ammonium formate (0.60 g, 9.5 mmol) was added to the reaction mixture, and stirring continued for 7 h. The mixture was absorbed onto silica gel by concentration *in vacuo*. Chromatography on silica gel, eluting with 0% to 20% MeOH in $CHCl_3$, and concentration afforded 0.61 g of the amidine as an off-white solid; mp 180-182 °C (dec); HRMS, e/z Calc. for $(M+H)^+$: 263.1144. Found: 263.1148.

administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

The term anti-coagulant agents (or coagulation inhibitory agents), as used herein, denotes agents that inhibit blood coagulation. Such agents include warfarin (available as Coumadin™) and heparin.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam. Piroxicam is commercially available from Pfizer Inc. (New York, NY), as Feldane™. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The phrase thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin and other inhibitors of thrombin synthesis such as Factor XA. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or

serotonin) and/or fibrin formation are disrupted. Such inhibitors include boroarginine derivatives and boropeptides, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471 651 A2, the disclosures of which are hereby incorporated herein by reference, in their entirety.

The phrase thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. Tissue plasminogen activator (tPA) is commercially available from Genentech Inc., South San Francisco, California. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosures of which are hereby incorporated herein by reference herein, in their entirety. Anistreplase is commercially available as Eminase™. The term urokinase,

as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

GPIIb/IIIa is known to be overexpressed in metastatic tumor cells. The compounds or combination products of the present invention may also be useful for the treatment, including prevention, of metastatic cancer.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the binding of fibrinogen to platelet GPIIb/IIIa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving GPIIb/IIIa. The compounds of the present invention may also be used in diagnostic assays involving platelet GPIIb/IIIa.

The compounds herein described may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention that contain asymmetrically substituted carbon atoms may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. All chiral,

diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

When any variable (for example but not limited to, R^2, R^4, R^6, R^7, R^8, R^{12}, and R^{14}, n, etc.) occurs more than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^4, then said group may optionally be substituted with up to two R^4 and R^4 at each occurrence is selected independently from the defined list of possible R^4. Also, by way of example, for the group $-N(R^{5a})_2$, each of the two R^{5a} substituents on N is independently selected from the defined list of possible R^{5a}. Similarly, by way of example, for the group $-C(R^7)_2-$, each of the two R^7 substituents on C is independently selected from the defined list of possible R^7.

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a bond joining a substituent to another group is not specifically shown or the atom in such other group to which the bond joins is not specifically shown, then such substituent may form a bond with any atom on such other group.

When a substituent is listed without indicating the atom *via* which such substituent is bonded to the rest of the compound of Formula I, then such substituent may be bonded *via* any atom in such substituent. For example, when the substituent is piperazinyl, piperidinyl, or tetrazolyl, unless specified otherwise, said piperazinyl, piperidinyl, tetrazolyl group may be bonded to the rest of the compound of Formula I *via* any atom in such piperazinyl, piperidinyl, tetrazolyl group.

Combinations of substituents and/or variables are permissible only if such combinations result in stable

compounds. By stable compound or stable structure it is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that any one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (for example, "C_1-C_{10}" denotes alkyl having 1 to 10 carbon atoms); "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-, bi-, or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantyl; and "bicycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or

branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

The terms "alkylene", "alkenylene", "phenylene", and the like, refer to alkyl, alkenyl, and phenyl groups, respectively, which are connected by two bonds to the rest of the structure of Formula I. Such "alkylene", "alkenylene", "phenylene", and the like, may alternatively and equivalently be denoted herein as "-(alkyl)-", "-(alkenyl)-" and "-(phenyl)-", and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean phenyl or naphthyl optionally substituted with 0-3 groups independently selected from methyl, methoxy, amino, hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; the term "arylalkyl" represents an aryl group attached through an alkyl bridge.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7- membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or an up to 26-membered polycyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocyles include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated,

partially unsaturated, or aromatic, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, isoxazolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl or octahydroisoquinolinyl, azocinyl, triazinyl, 6*H*-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, 1*H*-indazolyl, purinyl, 4*H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazole, carbazole, ß-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, phenarsazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl. Also

included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "heteroaryl" refers to aromatic heterocyclic groups. Such heteroaryl groups are preferably 5-6 membered monocylic groups or 8-10 membered fused bicyclic groups. Examples of such heteroaryl groups include, but are not limited to pyridyl (pyridinyl), pyrimidinyl, furanyl (furyl), thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, isoxazolyl, oxazolyl, pyrazinyl, pyridazinyl, benzofuranyl, benzothienyl, benzimidazolyl, quinolinyl, or isoquinolinyl.

As used herein, the term "chiral amine" refers to any amine containing compound that also contains a chiral center. Such compounds include, by way of example and without limitation, either enantiomer of cinchonidine, ephedrine, 2-phenylglycinol, 2-amino-3-methoxy-1-propanol, quinidine and pseudoephedrine.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of Formula I is modified by making acid or base salts of the compound of Formula I. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to Formula I *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of Formula I are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of Formula I wherein hydroxyl, amino, sulfhydryl, or carboxyl groups are bonded to any group that, when administered to a

mammalian subject, cleaves to form a free hydroxyl, amino, sulfhydryl, or carboxyl group respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of Formula I, and the like. Examples of representative carboxyl and amino prodrugs are included under the definition of R^2, R^3, and Y.

The pharmaceutically acceptable salts of the compounds of Formula I include the conventional non-toxic salts or the quaternary ammonium salts of the compounds of Formula I formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acids of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and

the like, or a quaternary ammonium hydroxide such as tetramethylammoinum hydroxide and the like.

As discussed above, pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid, respectively, in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The disclosures of all of the references cited herein are hereby incorporated herein by reference in their entirety.

Synthesis

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described in PCT Patent Application International Publication Number WO 95/14683 and the methods described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The following abbreviations are used herein:

β-Ala	3-aminopropionic acid
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
BOP	benzotriazolyl-N-oxytris(dimethylamino)-phosphonium hexafluorophosphate
BSTFA	*N,O*-bis(trimethylsilyl)trifluoromethyl-acetamide
Cbz	benzyloxycarbonyl
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DEC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DIEA	diisopropylethylamine
DCHA	dicyclohexylamine
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethyl alcohol
HOBt	1-hydroxybenzotriazole

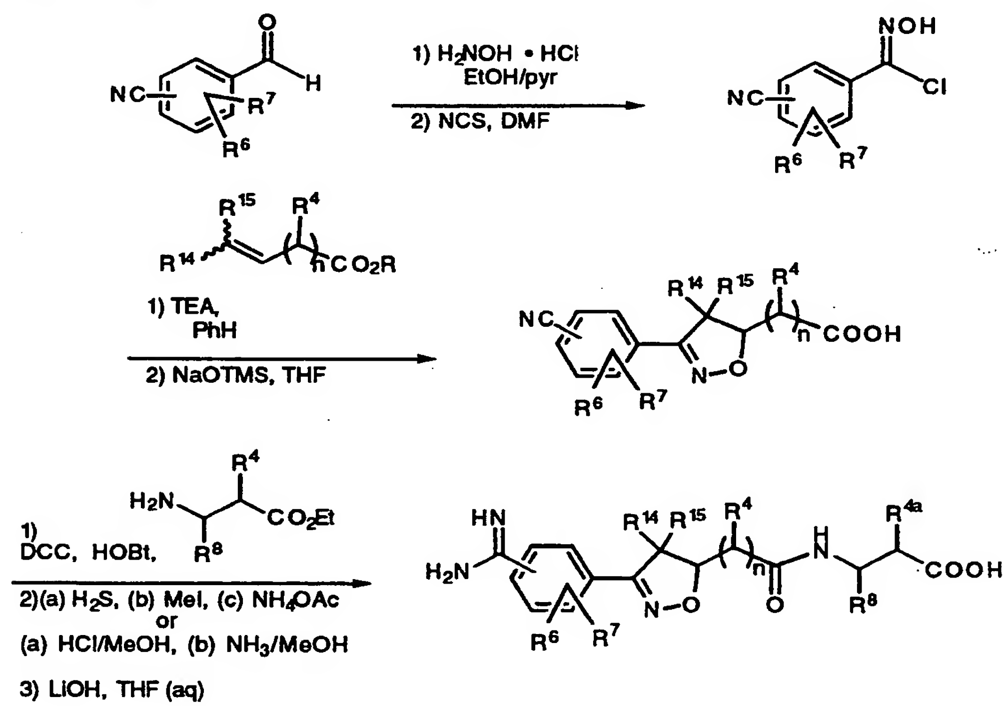
IBCF	*iso*-butyl chloroformate
LAH	lithium aluminum hydride
NCS	*N*-chlorosuccinimide
NMM	*N*-methylmorpholine
PPh_3	triphenylphosphine
pyr	pyridine
TBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

A convenient method for the synthesis of the compounds of this invention utilizes a dipolar cycloaddition of nitrile oxides with appropriate dipolarophiles to prepare the isoxazoline rings present in compounds of Formula I (for reviews of 1,3-dipolar cycloaddition chemistry, see 1,3-Dipolar Cycloaddition Chemistry (Padwa, ed.), Wiley, New York, 1984; Kanemasa and Tsuge, Heterocycles 1990, 30, 719).

Scheme I describes one synthetic sequence to the compounds of the second embodiment of this invention. An appropriately substituted hydroxylamine is treated with NCS in DMF according to the method of Liu, et al. (J. Org. Chem. 1980, 45, 3916). The resulting hydroximinoyl chloride is then dehydrohalogenated in situ using TEA to give a nitrile oxide, which undergoes a 1,3-dipolar cycloaddition to a suitably substituted alkene to afford the isoxazoline. Alternatively, the oxime may be oxidatively chlorinated, dehydrochlorinated and the resulting nitrile oxide trapped by a suitable alkene under phase transfer conditions according to the method of Lee (Synthesis 1982, 508). Hydrolysis of the ester using conventional methods known to one skilled in the art of organic synthesis gives the desired acids. Intermediates containing alkali-sensitive functionality, such as nitrile, may be deesterified with excellent

chemoselectivity using sodium trimethylsilanolate according to the procedure of Laganis and Ehenard (Tetrahedron Lett. 1984, 25, 5831). Coupling of the resulting acids to an appropriately substituted α- or β-amino ester using standard coupling reagents, such as DCC/HOBt, affords a nitrile-amide. The nitrile is then converted to the amidine *via* the imidate or thioimidate under standard conditions followed by ester saponification (LiOH, THF/H_2O).

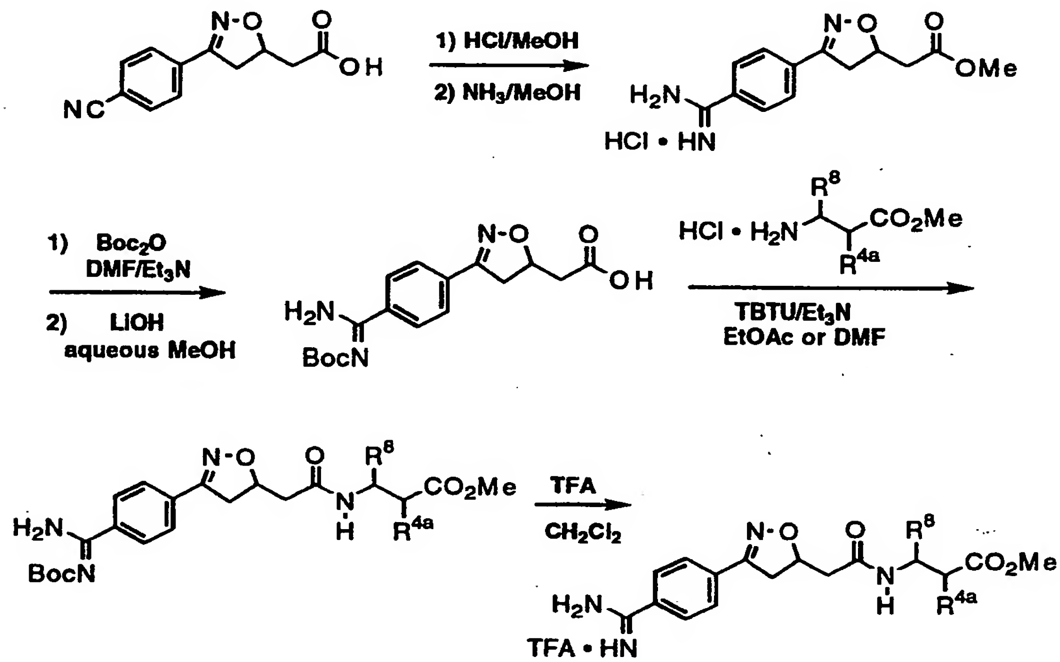
Scheme I



An example of a related method of preparation for compounds within the second embodiment of the present invention is illustrated in Scheme Ia. Conversion of 3-(4-cyanophenyl)isoxazolin-5-ylacetic acid to the corresponding amidine, followed by protection as the Boc-derivative and saponification provides 3-(4-Boc-amidinophenyl)isoxazolin-5-ylacetic acid which is coupled with β-amino acid esters as shown. Deprotection provides

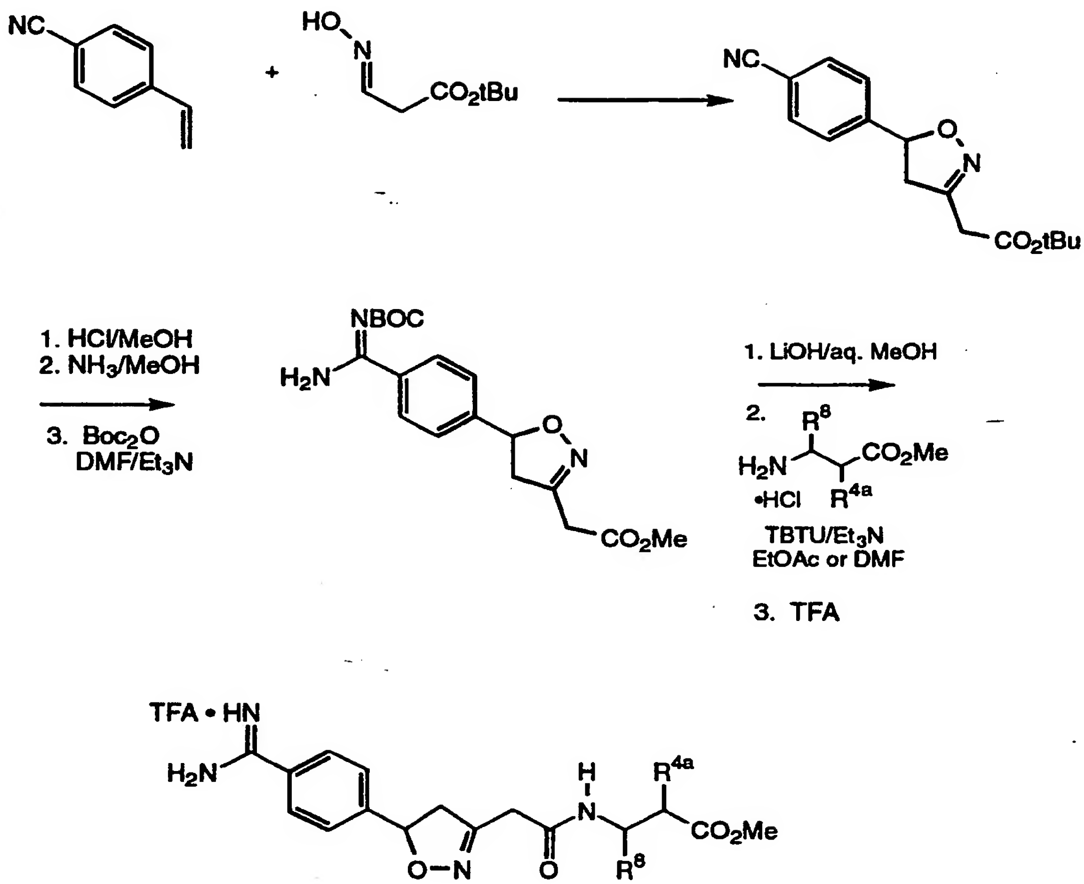
the desired isoxazolinylacetyl-β-aminoalaninyl esters. Saponification as described above gives the free acids.

Scheme Ia



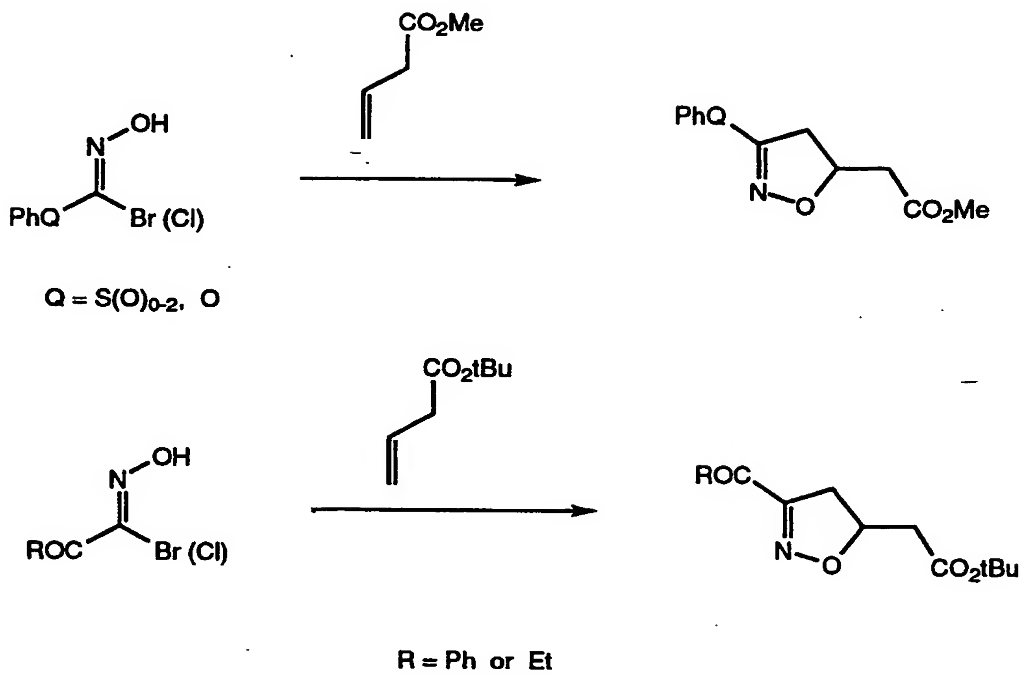
A further example of the synthesis of compounds within the second embodiment is shown in Scheme Ib. Cycloaddition of commerically available 4-cyanostyrene and t-butyl-3-oxoproprionate oxime using the method described by Gree et al. (Bioorganic and Med. Chem. Lett. 1994, 253) provides t-butyl [5-(4-cyanophenyl)isoxazolin-3-yl]acetate. Using the procedures described above, this intermediate is converted to compounds of formula I wherein the isoxazoline ring is in the reverse orientation with respect to the compounds prepared via Schemes I and Ia.

Scheme Ib



Additional isoxazolinyl acetates useful as starting materials for the preparation of compounds of Formula I, wherein V is -(phenyl)-Q- and Q is other than a single bond, can be prepared by cycloaddition of a suitably substituted chloro or bromooxime with an ester of vinyl acetic acid as shown in Scheme Ic using literature methods or modifications thereof. (D. P. Curran & J. Chao, J. Org. Chem. 1988, 53, 5369-71; J. N. Kim & E. K. Ryu, Heterocycles 1990, 31, 1693-97).

Scheme Ic

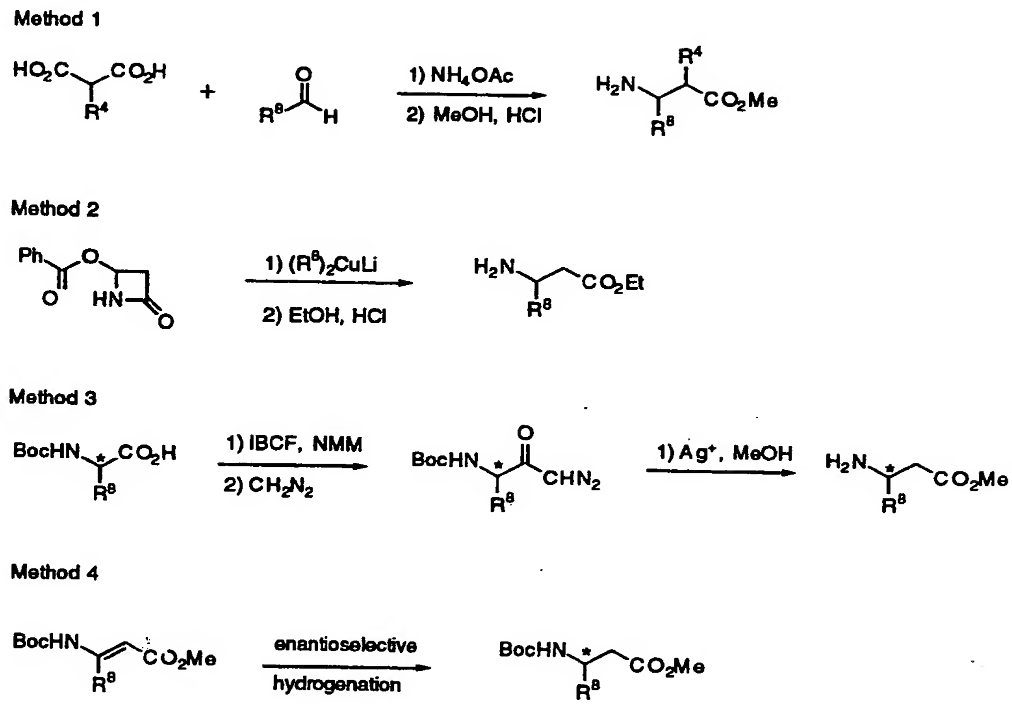


The compounds of the present invention where R^2 or R^3 is e.g. alkoxycarbonyl may be prepared by reacting the free amidines, amines or guanidines with an activated carbonyl derivative, such as an alkyl chloroformate. In compounds of the second embodiment, the conversion of the free amines, amidines and guanidines to such acyl-nitrogen groups may optionally be performed prior to coupling an isoxazoline acetic acid with e.g β-amino acids, as illustrated in Scheme Ia.

The compounds of the present invention wherein Y is an oxyalkoxy group, e.g. alkoxycarbonyloxyalkoxy, may be prepared by reacting a suitably protected carboxylic acid of Formula I with an alkoxycarbonyloxyalkyl chloride in the presence of an iodide source, such as tetrabutylammonium iodide or potassium iodide, and an acid scavenger, such as triethylamine or potassium carbonate, using procedures known to those skilled in the art.

The appropriately substituted racemic β-amino acids may be purchased commercially or, as is shown in Scheme II, Method 1, prepared from the appropriate aldehyde, malonic acid and ammonium acetate according to the procedure of Johnson and Livak (J. Am. Chem. Soc. 1936, 58, 299). Racemic β-substituted-β-amino esters may be prepared through the reaction of dialkylcuprates or alkyllithiums with 4-benzoyloxy-2-azetidinone followed by treatment with anhydrous acid in ethanol (Scheme I, Method 2) or by reductive amination of β-keto esters as is described in WO9316038. (Also see Rico et al., J. Org. Chem. 1993, 58, 7948-51.) Enantiomerically pure β-substituted-β-amino acids can be obtained through the optical resolution of the racemic mixture or can be prepared using numerous methods, including: Arndt-Eistert homologation of the corresponding α-amino acids as shown in Scheme II, Method 3 (see Meier, and Zeller, Angew. Chem. Int. Ed. Engl. 1975, 14, 32; Rodriguez, et al. Tetrahedron Lett. 1990, 31, 5153; Greenlee, J. Med. Chem. 1985, 28, 434 and references cited within); and through an enantioselective hydrogenation of a dehydroamino acid as is shown in Scheme II, Method 4 (see Asymmetric Synthesis, Vol. 5, (Morrison, ed.) Academic Press, New York, 1985). A comprehensive treatise on the preparation of β-amino acid derivatives may be found in patent application WO 9307867, the disclosure of which is hereby incorporated by reference.

Scheme II

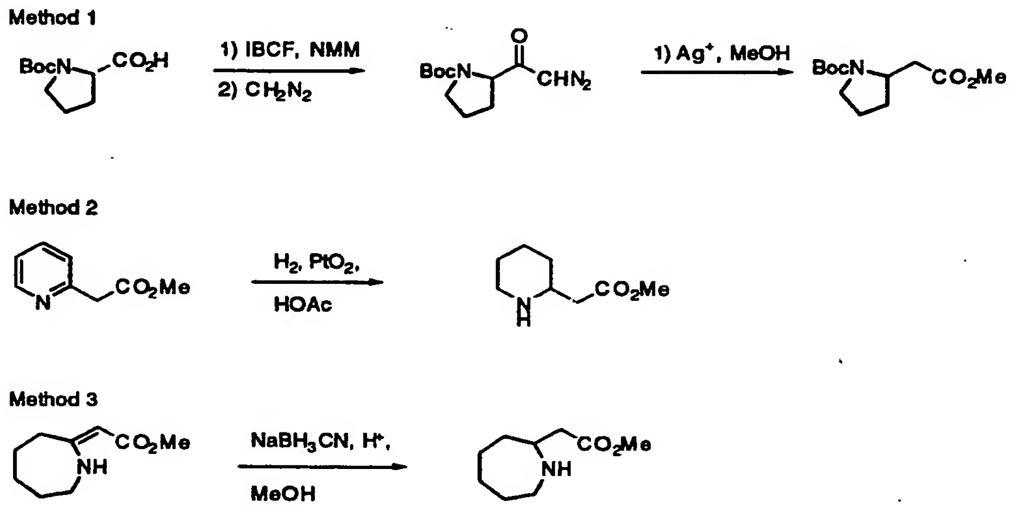


The synthesis of N^2-substituted diaminopropionic acid derivatives can be carried out via Hoffman rearrangement of a wide variety of asparagine derivatives as described in Synthesis, 266-267, (1981).

The appropriately substituted pyrrolidine-, piperidine- and hexahydroazepineacetic acids may be prepared using a number of methods. The pyrrolidines are conveniently prepared using an Arndt-Eistert homologation of the corresponding proline as shown in Scheme III, Method 1 (see Meier, and Zeller, Angew. Chem. Int. Ed. Engl. 1975, 14, 32; Rodriguez, et al. Tetrahedron Lett. 1990, 31, 5153; Greenlee, J. Med. Chem. 1985, 28, 434 and references cited within). The piperidines can be prepared by reduction of the corresponding pyridine as shown in Scheme III, Method 2. The hexahydroazepines are prepared by reduction of the corresponding vinylogous amide using

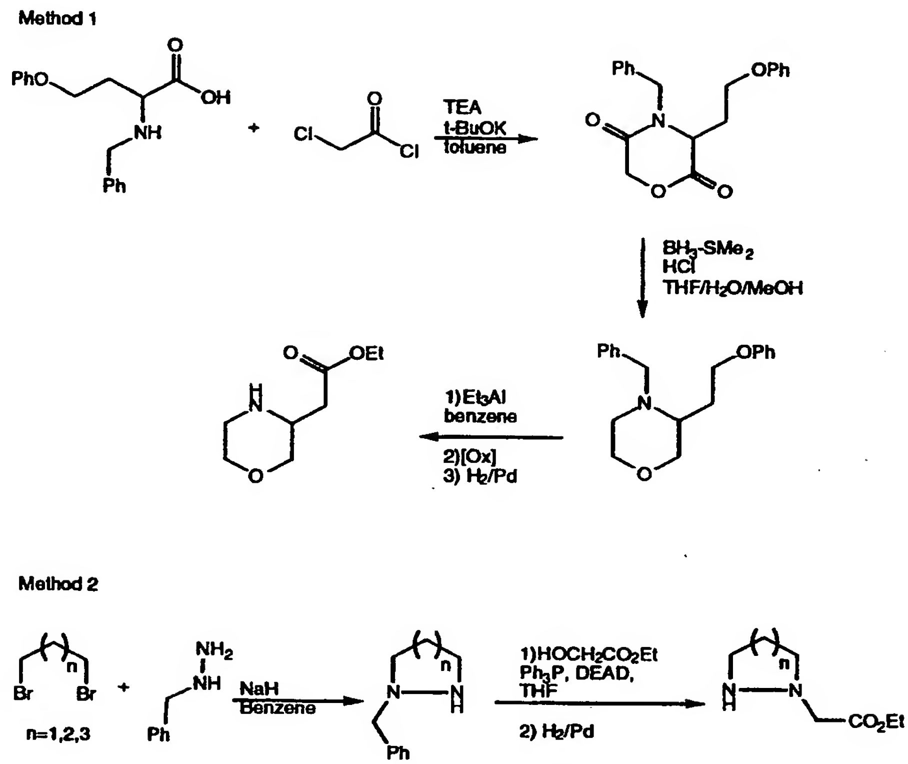
sodium cyanoborohydride as depicted in Scheme III, Method 3.

Scheme III



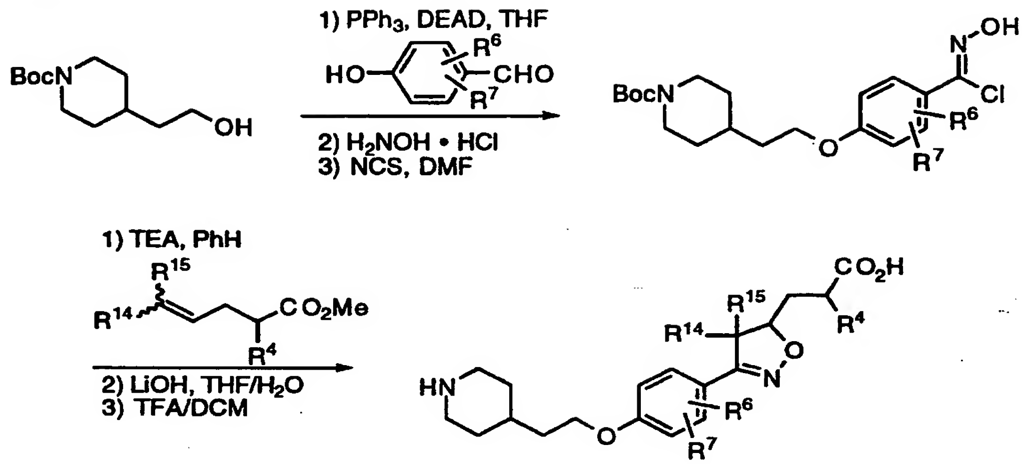
Many additional appropriately substituted heterocycles are available commercially or can be readily modified by procedures known by one skilled in the art. Appropriately substituted morpholines can be prepared from amino acids via the sequence of steps depicted in Scheme IIIa, method 1(see Brown, et. al. *J. Chem. Soc. Perkin Trans I* **1987**, 547; Bettoni, et. al. *Tetrahedron* **1980**, *36*, 409; Clarke, F.H. *J. Org. Chem.* **1962**, *27*, 3251 and references therein.) N-ethoxycarbonylmethyl-1,2-diazaheterocyles are prepared by condensation of suitably substituted dibromides with benzylhydrazine followed by Mitsunobu reaction with ethyl hydroxyacetate and deprotection as shown in Scheme IIIa, method 2 (see Kornet, et. al. J. Pharm. Sci. 1979, 68, 377.; Barcza, et. al. J. Org. Chem. 1976, 41, 1244 and references therein.)

Scheme IIIa



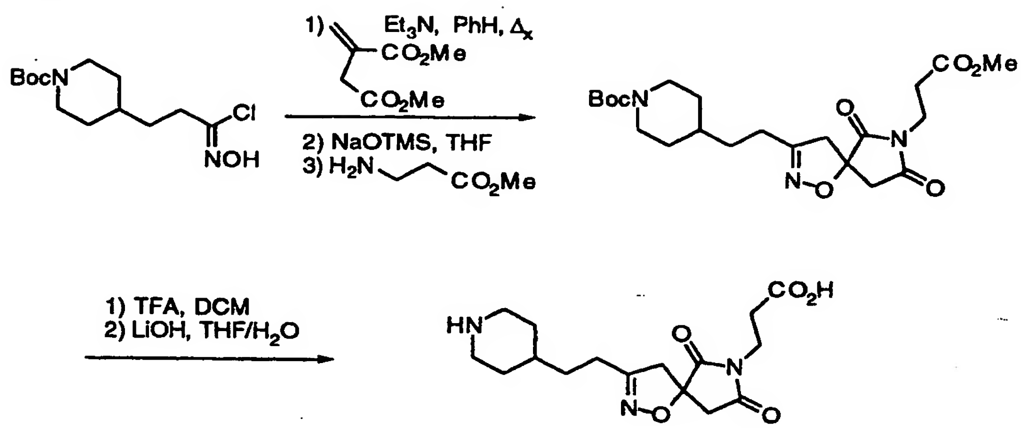
A general synthetic protocol to the compounds of the first embodiment of this invention is depicted in Scheme IV. Coupling of a suitable Boc-protected amino alcohol to an appropriately substituted phenol under Mitsunobu conditions (see Mitsunobu, Synthesis 1981, 1) is followed by oximation using hydroxylamine hydrochloride in 1:1 ethanol/pyridine. Isoxazoline formation, ester saponification and Boc-deprotection (33% TFA/DCM) then affords the compounds of this invention in good overall yield.

Scheme IV



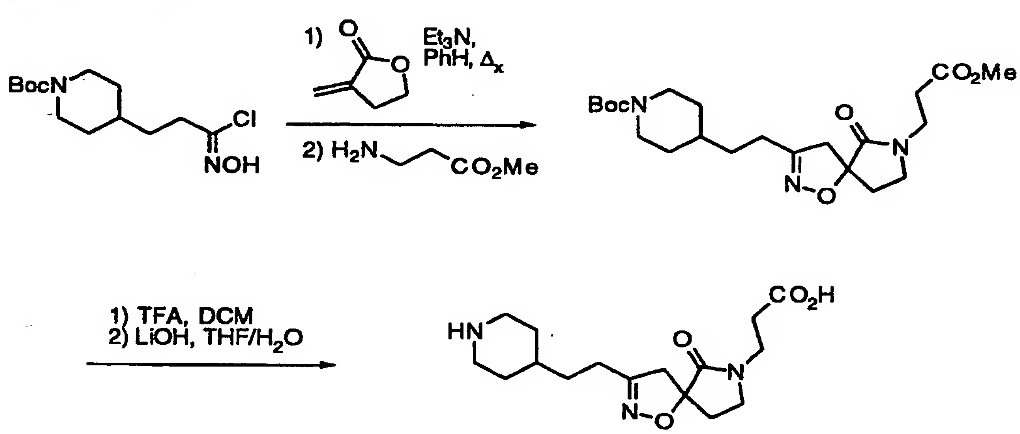
The synthesis of the spiro-fused isoxazolinyl imides of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme V. Dipolar cycloaddition of an oximinoyl chloride with a α-methylene diester affords an isoxazolinyl diester, which is deesterified using the silanolate method. Dehydration to the anhydride according to Ishihara, et al. (Chem. Pharm. Bull. 1992, 40, 1177-85) followed by imide formation using an appropriately substituted amino ester affords the spirocycle. Alternatively, the imide may be prepared directly from the isoxazoline diester according to Culbertson, et al. (J. Med. Chem. 1990, 33, 2270-75). Amidine formation or Boc deprotection followed by ester saponification then affords the compounds of this invention in good overall yield.

Scheme V



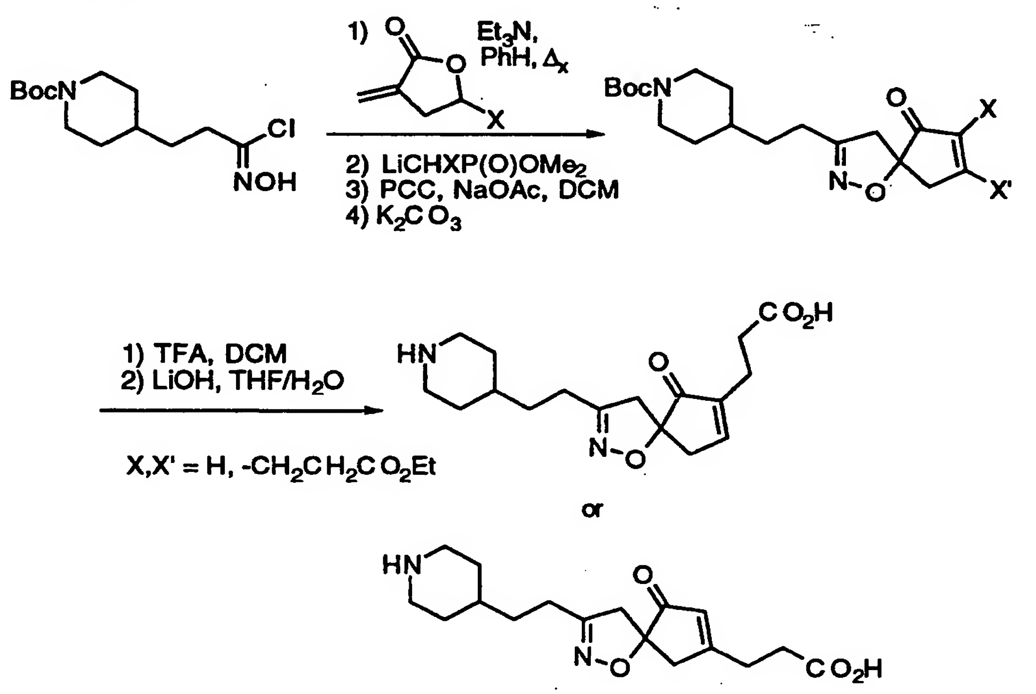
The synthesis of the spiro-fused isoxazolinyl amides of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme VI. Dipolar cycloaddition of an oximinoyl chloride with a α-methylene lactone affords the isoxazolinyl lactone, which is reacted with an appropriate amino ester to afford the amide (see The Chemistry of the Amides (Zabicky, ed.), p 96, Interscience, New York, 1970; Prelog, et al., Helv. Chim. Acta 1959, 42, 1301; Inubushi, et al., J. Chem. Soc., Chem. Commun. 1972, 1252). Amidine formation or Boc deprotection followed by ester saponification then affords the compounds of this invention in good overall yield.

Scheme VI



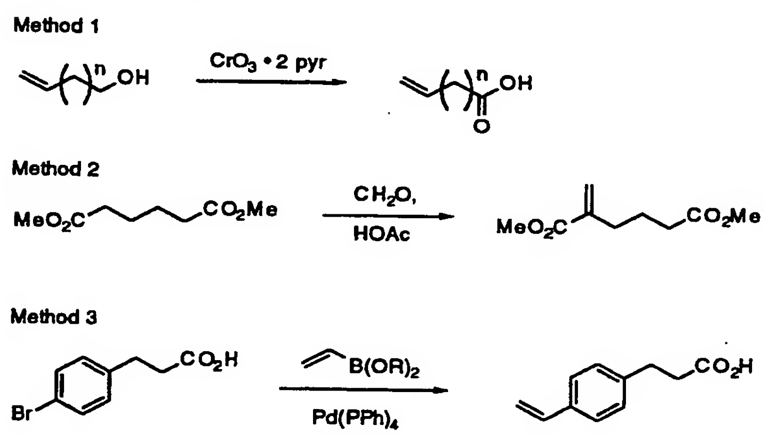
The synthesis of the spiro-fused isoxazolinyl cycloalkenes of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme VII. Dipolar cycloaddition of an oximinoyl chloride with an appropriately substituted α-methylene lactone affords the isoxazolinyl lactone. The lactone is then reacted with an appropriate lithium dimethyl alkylphosphonate, followed by PCC oxidation. The resulting diketophosphonate undergoes an intramolecular Wittig reaction in the presence of K_2CO_3/18-crown-6 according to the method described by Lim and Marquez (Tetrahedron Lett. 1983, 24, 5559). Amidine formation or Boc deprotection followed by ester saponification then affords the compounds of this invention in good overall yield.

Scheme VII



The dipolarophiles used to prepare the compounds of this invention may be prepared by numerous methods. The ω-alkenoic ester class of dipolarophile may be purchased commercially or prepared by oxidation of the corresponding ω-alkenols by the method of Corey and Schmidt (Tetrahedron Lett. 1979, 399, Scheme VIII, Method 1). The α-methylene diester and α-methylene lactone class of dipolarophile may be purchased commercially or can be prepared by numerous methods from the corresponding diester (see Osbond, J. Chem. Soc. 1951, 3464; Ames and Davey, J. Chem. Soc. 1958, 1794; Vig, et al., Ind. J. Chem. 1968, 6, 60; Grieco and Hiroi, J. Chem. Soc., Chem. Commun. 1972, 1317, Scheme VIII, Method 2). The 3-(styryl)propionic ester class of dipolarophile may be prepared by palladium-catalyzed cross coupling of the appropriately substituted bromo- or iodohydrocinnamic acid to a vinylmetal species according to methods cited within Mitchell (Synthesis 1992, 803) and Stille (Angew. Chem. Int. Ed. Engl. 1986, 25, 508, Scheme VIII, Method 3).

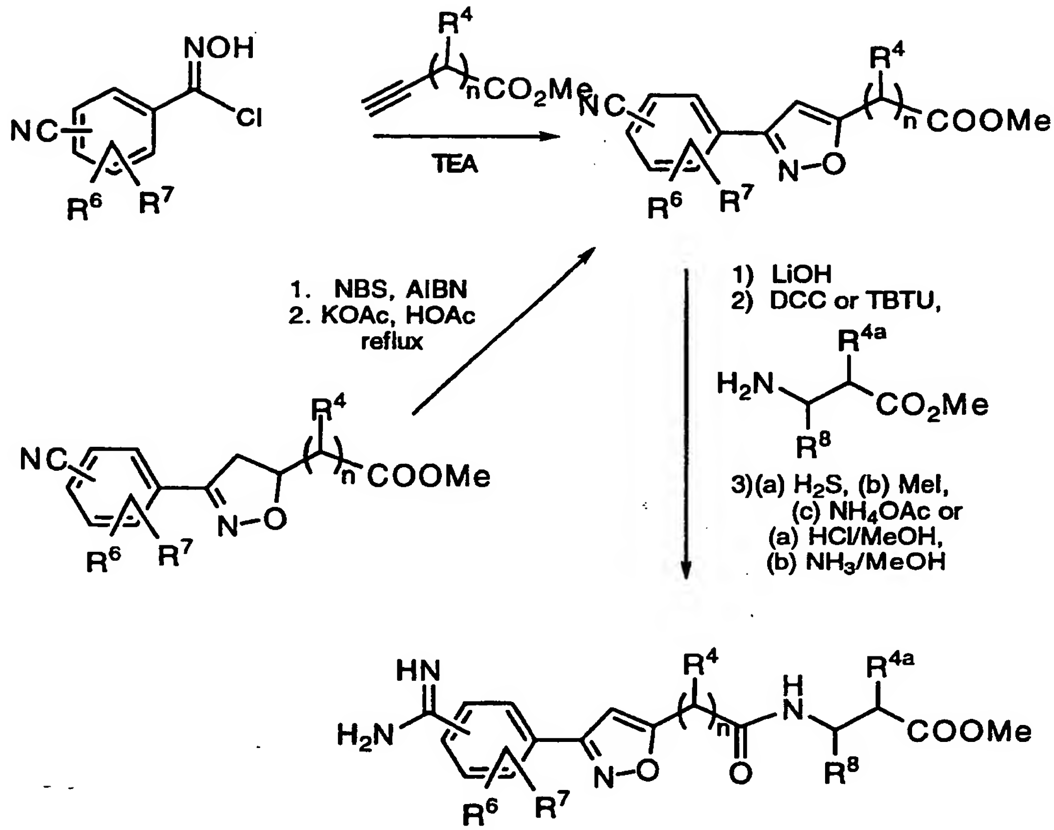
Scheme VIII



Compounds of Formula I wherein b is a double bond can be prepared using one of the routes depicted in Scheme IX. Bromination followed by subsequent dehydrobromination of a suitably substituted methyl 3-(cyanophenyl)isoxazolin-5-ylacetate, prepared as described above, using the method

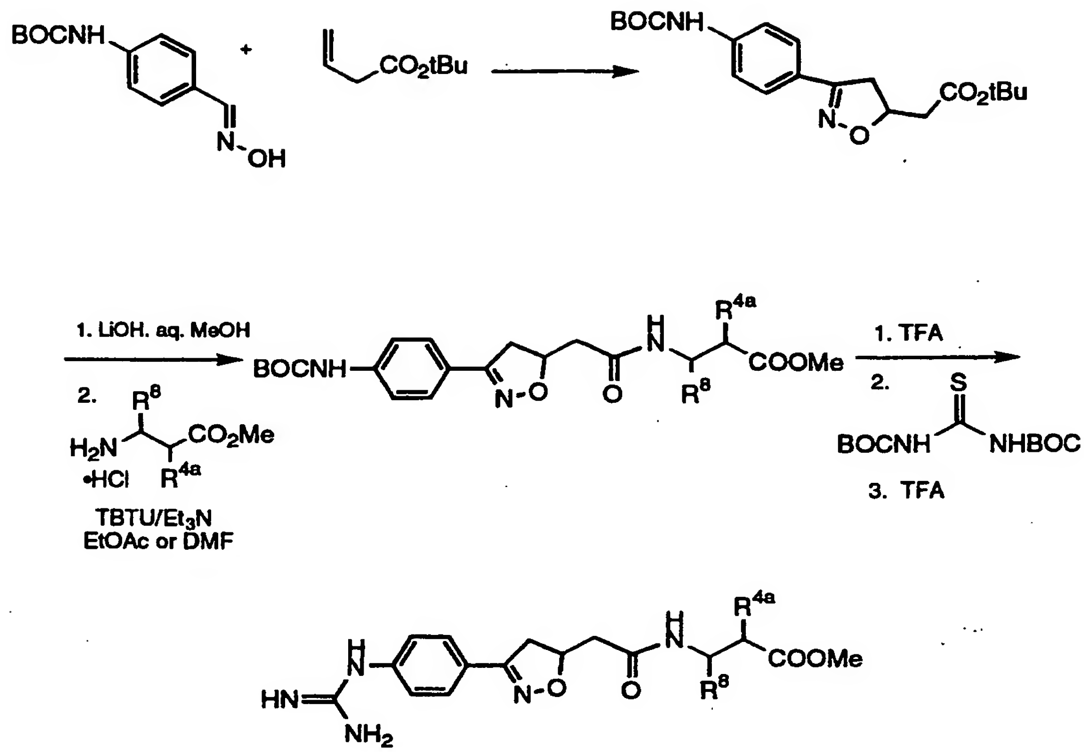
of Elkasaby & Salem (Indian J. Chem. **1980**, *19B*, 571-575) provides the corresponding isoxazole intermediate. Alternately, this intermediate can be obtained by 1,3-dipolar cycloaddition of a cyanophenylnitrile oxide (prepared from the corresponding chlorooxime as described in Scheme I) with an appropriate alkyne to give the isoxazole directly. Hydrolysis of the ester using conventional methods known to one skilled in the art of organic synthesis gives the acetic acids. Coupling of the resulting acids to an appropriately substituted α- or β-amino ester using standard coupling reagents, such as TBTU, affords a nitrile-amide. The nitrile is then converted to the amidine *via* the imidate or thioimidate under standard conditions to give the prodrug esters. Saponification gives the acids.

Scheme IX



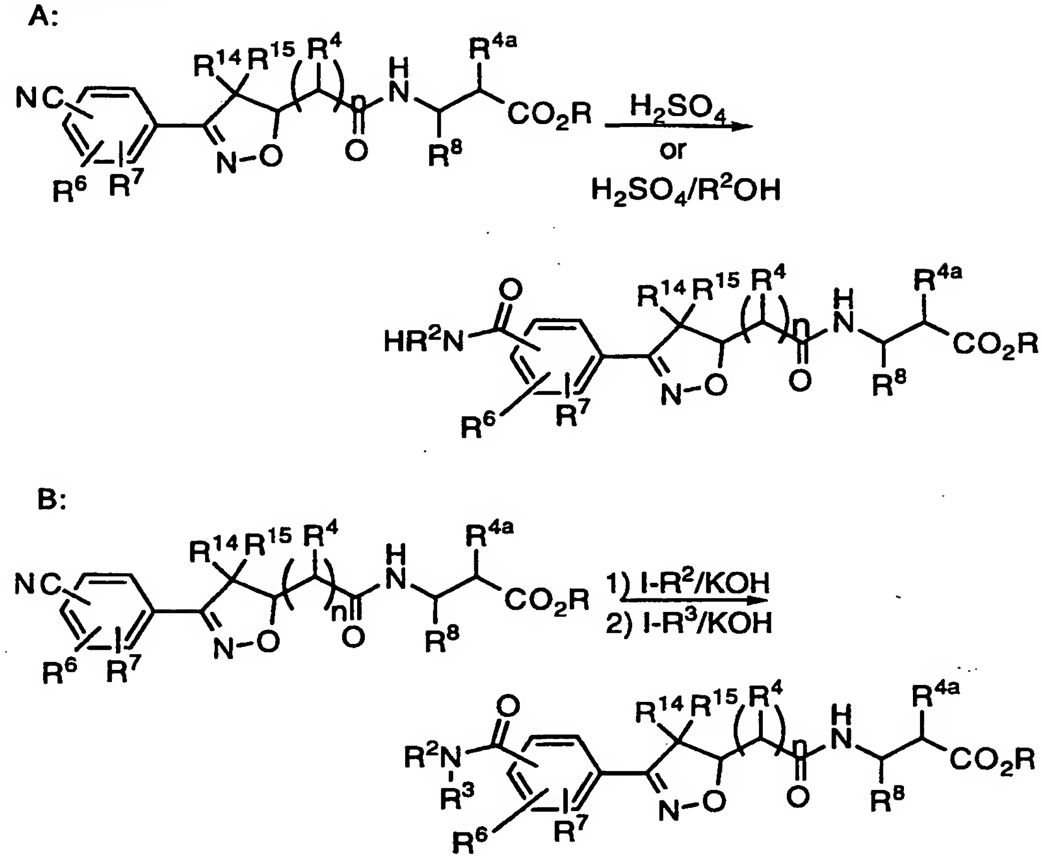
Compounds of Formula I wherein R^1 is $(R^2)(R^3)N(R^2N=)CN(R^2)$- and V is phenylene are prepared as illustrated in Scheme X. Cycloaddition of an appropriately N-protected aminophenylaldoxime with vinyl acetic acid, t-butyl ester, using the conditions described above provides t-butyl [3-(4-t-butyloxycarbonylaminophenyl)isoxazolin-5-yl]acetate. Hydrolysis of the ester with lithium hydroxide provides the free acid which can be coupled with a suitably substituted methyl 3-aminopropionate as previously described. After deprotection, the aniline is converted to the corresponding guanidine using the method described by Kim et al. (Tetrahedron Lett. 1993, 48, 7677). A final deprotection step to remove the BOC groups provides guanidino compounds of Formula I.

Scheme X



An example of the preparation of compounds of the second embodiment wherein R^1-U is a benzamide is illustrated in Scheme XI. Conversion of the 3-(4-cyanophenyl)isoxazolin-5-yl-β-aminoalaninyl esters to the amides can be accomplished by reaction of the nitrile with an appropriate alcohol under acidic conditions. (J. Med. Chem. 1991, 34, 851.) The substituted amides can be accessed by allowing the 3-(4-cyanophenyl)isoxazolin-5-yl-β-aminoalaninyl esters to react with an appropriate halogenated compound (Synthesis, 1978, 303. Saponification as described above gives the free acids.

Scheme XI



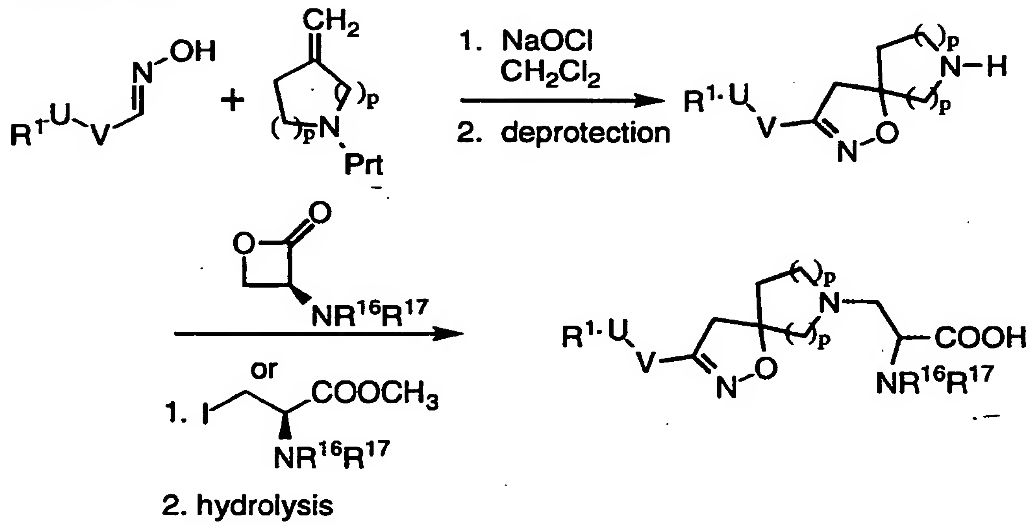
The compounds of the invention where U is a pyridyl may be prepared by several methods. 2-Amino-4-pyridyl analogs can be easily accessed from readily available 2-bromo-4-pyridylcarboxaldehyde (Corey, E.J et. al. Tetrahedron Lett. 1983, 32, 3291). The desired amino compound can be suitably introduced by displacement of the bromo substituent with a suitable ammonia source or alternatively with sodium azide followed by reduction via standard techniques known to those in the art. 2-Amidino-5-pyridyl analogs can be accessed from 2-bromo-5-pyridylcarboxaldehyde by displacement of the bromide at an appropriate stage in the synthesis with KCN. Conversion of the nitrile to the requisite amidine then affords the desired products. 6-Amino-3-pyridyl analogs can be easily accessed (according to the method described for the

preparation of 2-amino-5-pyridyl analogs) from 6-chloro-3-pyridylcarboxaldehyde. This was obtained in part from 6-chloro-3-pyridylcarboxylic acid (Aldrich) via techinques known in the art. 6-Amidino-3-pyridyl analogs can be readily accessed from 6-chloro-3-pyridylcarboxaldehyde via techniques described for 2-amidino-5-pyridylanalogs.

The preparation of quinuclidine carboxaldehyde starting materials may be done as follows. 4-Cyanoquinuclidine prepared by the method of Kanai,T. et al, (Het., 1992, 34, 2137), can be converted to quinuclidine-4-carboxaldehyde by standard conditions and homologated by the method of (Tetrahedron Lett. 1987, 28, 1847) to the desired aldehyde. Conversion of the aldehyde to the oxime followed by chlorination to the chlorooxime should then afford the key quinuclidine chlorooxime which can then be further elaborated to the desired compounds.

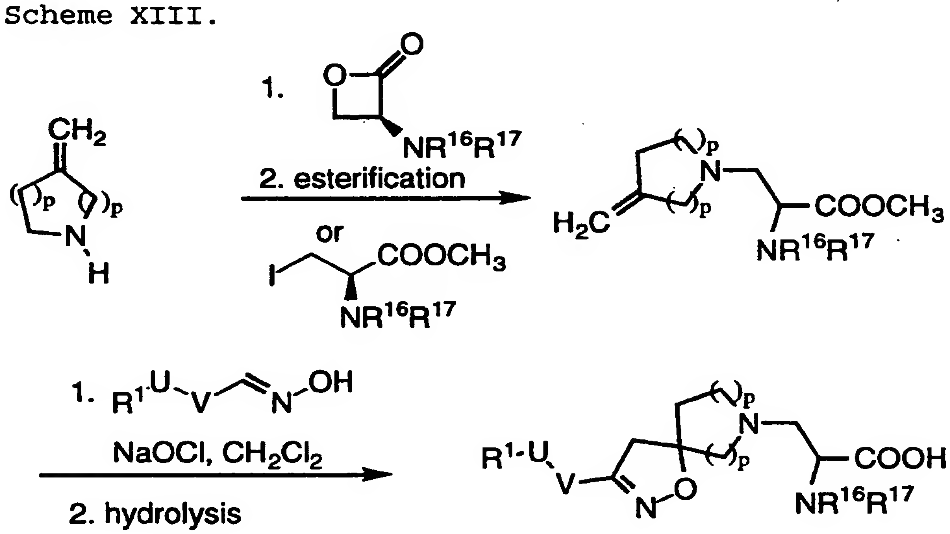
The synthesis of spiro-fused isoxazolinyl amines of the third embodiment of the present invention is exemplified by the general protocol depicted in Scheme XII. Dipolar cycloaddition of a suitable oxime with a suitably protected methylenecycloamine, prepared by methods known in the literature (De Amici, M.; Frølund, B.; Hjeds, H.; Krogsgaard-Larson, P. *Eur. J. Med. Chem.* **1991**, *26*, 625; Mimura, M., *et. al. Chem. Pharm. Bull.* **1993**, *41*, 1971; Labouta, I. M.; Jacobsen, P.; Thorbek, P.; Krogsgaard-Larson, P.; Hjeds, H. *Acta Chem. Scand., Ser. B* **1982**, *36*, 669), yields the spirocyclic amine after deprotection. This amine can be functionalized with a serine beta-lactone (Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* ***1985***, *107*, 7105) providing an optically active product. Alternatively, the amine can be reacted with a 3-iodo or 3-chloroalanine derivative (I: Märki, W.; Schwyzer, R. *Helv. Chim. Acta* **1975**, *58*, 1471; Cl: Bigge, C. F.; Wu J.-P.; Drummond, J. R. *Tetrahedron Lett.* **1991**, *32*, 7659; Benoiton, L. *Can. J. Chem.* **1968**, *46*, 1549) to give a racemic product.

Scheme XII.



The cycloaddition can also be performed after the introduction of the propionyl side chain as shown in Scheme XIII.

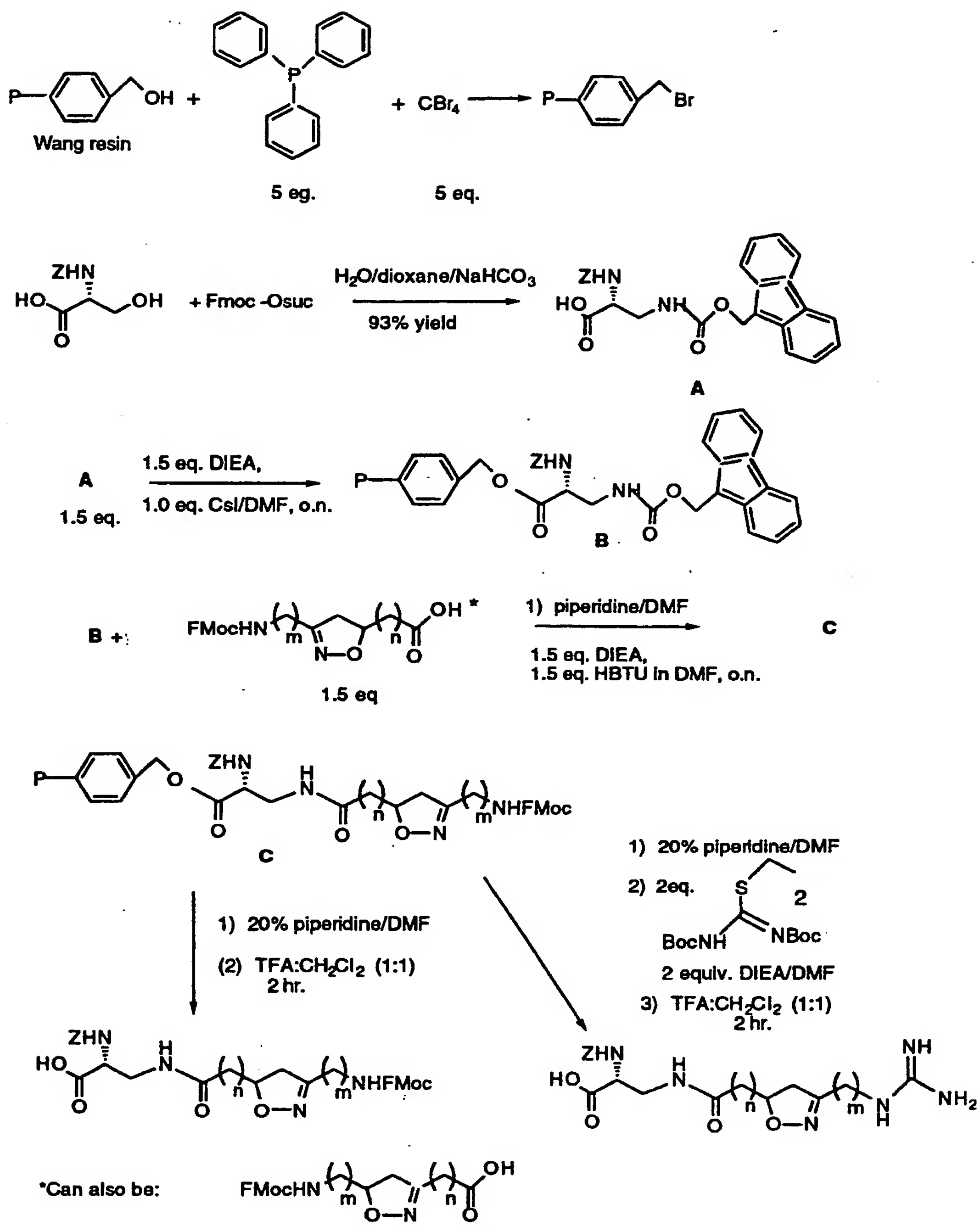
Scheme XIII.



The compounds of Tables 12 and 13 were made using combinatorial synthetic methodology as shown in Scheme XIV. Thus, a resin was derivatized and to it was coupled the protected 2,3-diaminoproprionate. Following

deprotection of N^3, the desired isoxazoline carboxylic acid was coupled to N^3. The final product was removed from once the terminal amine of the isoxazoline carboxylic acid was converted to its desired form.

Scheme XIV.



The compounds of this invention and their preparation can be further understood by the following procedures and examples, which exemplify but do not constitute a limit of their invention.

Example 43

N-[3-(4-Amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*R,S*)-3-amino-3-phenylpropanoic Acid

Part A: 4-Cyanobenzaldoxime

This material was prepared from 4-cyanobenzaldehyde according to Kawase and Kikugawa (J. Chem. Soc., Perkin Trans I 1979, 643). To a solution of 4-cyanobenzaldehyde (1.31 g, 10 mmol) in 1 : 1 EtOH : pyridine (10 mL) was added hydroxylamine hydrochloride (0.70 g, 10 mmol). The resulting solution was stirred at room temperature for 18 h and was concentrated *in vacuo* to one-half volume. To this solution was added ice water, causing the product to crystallize from solution. Recrystallization from EtOH - water followed by drying over P_2O_5 afforded 1.46 g (100%) of the desired oxime; mp: 167.8-169.4 °C.

Part B: Methyl 3-(3-Butenoyl)amino-3-phenylpropionate

To a solution of vinylacetic acid (861 mg, 10.0 mmol), methyl 3-amino-3-phenylpropionate hydrochloride (2.37 g, 11.0 mmol) and TEA (1.6 mL, 12 mmol) in DCM (20 mL) at -10 °C was added DEC (2.11 g, 11.0 mmol). The resulting mixture was stirred at -10 °C for 15 hours. The mixture was then washed with water, 0.1 *M* HCl, sat. $NaHCO_3$, sat. NaCl and dried over anhydrous $MgSO_4$. Concentration *in vacuo* followed by pumping until constant weight gave 2.36 g (95%) of the desired amide as a golden oil of suitable purity for further reaction; ^1H NMR (300 MHz, $CDCl_3$) δ7.28 (m, 5H), 6.78 (bd, J = 7.7 Hz, 1H), 5.95 (m, 1H), 5.43 (dt, J = 8.4, 5.9 Hz, 1H), 5.25 (m, 2H), 3.61 (s, 3H), 3.04 (d, J = 7.0 Hz, 2H), 2.88 (dq, J = 15.0, 5.9 Hz, 2H).

Part C: Methyl 3(*R,S*)-{5(*R,S*)-N-[3-(4-Cyanophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoate

To a solution of methyl 3-(3-butenoyl)amino-3-phenylpropionate (816 mg, 3.30 mmol) and 4-cyanobenzaldoxime (prepared according to Example 1, Part A, 438 mg, 3.00 mmol) in CH_2Cl_2 (10 mL) was added a 5% solution of sodium hypochlorite ("Clorox", 5.3 mL, 3.5 mmol). The resulting mixture was stirred rapidly overnight (15 h), the layers separated and the aqueous washed with CH_2Cl_2. The combined organic was dried (MgSO4) and concentrated *in vacuo*. The crude product was then purified using flash chromatography (70% EtOAc/hexanes), affording 731 mg (62%) of the desired isoxazoline as a 1 : 1 mixture of diastereomers; ^1H NMR (300 MHz, $CDCl_3$) δ7.74 (m, 8H), 7.29 (m, 10H), 6.92 (bm, 2H), 5.42 (m, 2H), 5.16 (m, 2H), 3.64 (s, 3H), 3.60 (s, 3H), 3.48 (m, 2H), 3.26 (dd, J = 17.3, 7.7 Hz, 1H), 3.15 (dd, J = 16.8, 8.1 Hz, 1H), 2.85 (m, 2H), 2.69 (m, 2H).

Part D: Methyl 3(*R,S*)-{5(*R,S*)-N-[3-(4-Amidinophenyl)isoxazo-lin-5-ylacetyl]amino}-3-phenylpropanoate

Into a solution of methyl 3(*R,S*)-{5(*R,S*)-N-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoate (587 mg, 1.50 mmol) in 10% DCM/methanol (55 mL) was bubbled dry HCl gas for 2 hours. The mixture was stirred for 18 hours, then concentrated *in vacuo*. The crude imidate was dissolved in methanol (20 mL) and ammonium carbonate added. The resulting mixture was stirred for 18 hours, then filtered. The filtrate was concentrated *in vacuo* and the residue purified using flash chromatography ($CHCl_3$ - 20% methanol/$CHCl_3$). Concentration of the appropriate fractions *in vacuo* followed by placing the residue under vacuum until constant weight afforded 193 mg (32%) of the desired amidines; CIMS (NH_3, e/z, relative abundance): 409 $(M + H)^+$, 100%.

Part E: 3(*R,S*)-{5(*R,S*)-N-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoic Acid, Trifluoroacetic Acid Salt

Methyl 3(*R,S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoate (45 mg, 0.113 mmol) was saponified using 0.5 *M* LiOH (0.6 mL, 0.3 mmol) according to Example 1, Part F, affording 28 mg (49%); CIMS (NH_3, e/z, relative abundance): 412 $(M + H)^+$, 100%.

Example 43A

5(*R,S*)-N-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]aminopropanoic Acid

Part A: Ethyl 3-(3-Butenoyl)aminopropionate

To an ice cold solution of vinylacetic acid (4.39 g, 51.0 mmol), ethyl 3-aminopropionate hydrochloride (8.49 g, 55.3 mmol) and TEA (7.8 mL, 56 mmol) in DCM (50 mL) was added DEC (10.54 g, 55.0 mmol). The resulting mixture was warmed to room temperature overnight (18 h). The mixture was then washed with water, 0.1 *M* HCl, sat. $NaHCO_3$, sat. NaCl and dried ($MgSO_4$). Concentration *in vacuo* followed by pumping until constant weight was achieved gave 6.34 g (67%) of the desired amide as a golden oil of purity suitable for further reaction; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (bs, 1H), 5.98-5.85 (m, 1H), 5.25-5.17 (m, 2H), 4.16 (q, J = 7.0 Hz, 2H), 3.52 (q, J = 5.9 Hz, 2H), 2.99 (dt, J = 7.0, 1.1 Hz, 2H), 2.53 (t, J = 5.9 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H).

Part B: Ethyl 5(*R,S*)-N-[3-(4-Cyanophenyl)isoxazolin-5-ylacetyl]aminopropanoate

To a solution of ethyl 3-(3-butenoyl)aminopropionate (556 mg, 3.00 mmol) and 4-cyanobenzaldoxime (prepared according to Example 1, Part A, 292 mg, 2.00 mmol) in CH_2Cl_2 (7 mL) was added a 5% solution of sodium

hypochlorite ("Clorox", 4.2 mL, 2.8 mmol). The resulting mixture was stirred rapidly overnight (15 h), the layers separated and the aqueous washed with CH_2Cl_2. The combined organic was dried (MgSO4) and concentrated *in vacuo*. The crude product was then purified using flash chromatography (EtOAc), affording 386 mg (58%) of the desired isoxazoline; mp: 102.0-102.9 °C.

Part C: Ethyl 5(*R,S*)-3-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]aminopropanoate

Into a solution of ethyl 5(*R,S*)-3-[3-(4-cyanophenyl)isoxazolin-5-ylacetyl]aminopropanoate (1.65 mg, 5.00 mmol) in 10% DCM/EtOH (165 mL) was bubbled HCl gas for 2 hours. After 18 hours, the solvent was evaporated *in vacuo*, the residue dissolved in EtOH (100 mL) and ammonium carbonate (14.41 g, 150 mmol) added. The resulting suspension was stirred at room temperature for 18 hours, then filtered and the resulting filtrate concentrated *in vacuo*. The residue was then crystallized from EtOH/ether, giving 713 mg (41%) of the desired amidine; ^{1}H NMR (300 MHz, CD_3OD) δ 7.88 (AB quartet, Δ = 16.8 Hz, J = 8.4 Hz, 4H), 5.13 (m, 1H), 4.12 (q, J = 7.3 Hz, 2H), 3.58 (dd, J = 17.2, 10.6 Hz, 1H), 3.44 (m, 2H), 3.26 (dd, J = 17.2, 7.3 Hz, 1H, coincident with solvent), 2.57 (m, 4H), 1.25 (t, J = 7.3 Hz, 2H).

Part H: 5(*R,S*)-3-[3-(4-Amidinophenyl)isoxazolin-5-ylacetyl]aminopropanoic Acid

To a solution of ethyl 5(*R,S*)-3-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]aminopropanoate (346 mg, 1.00 mmol) in EtOH (6 mL) was added 0.5 *M* LiOH. Upon mixing, a precipitate of the zwitterionic product began to form. After stirring for 18 hours at room temperature, the solid was collected by filtration, affording 365 mg of the title compound; ^{1}H NMR (300 MHz, CD_3OD) δ 7.86 (AB quartet, Δ = 18.3 Hz, J = 8.4 Hz, 4H), 5.21 (m, 1H), 3.57 (dd, J =

17.2, 10.6 Hz, 1H), 3.43 (m, 2H), 3.25 (dd, J = 17.2, 7.3 Hz, 1H, coincident with solvent), 2.64 (dd, J = 14.6, 6.8 Hz, 1H), 2.52 (m, 3H).

Example 278a

Methyl N^2-n-butyloxycarbonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(R)-ylacetyl]-(S)-2,3-diaminopropionate Mesylate salt.

Methyl N^2-n-butyloxycarbonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(R)-ylacetyl]-(S)-2,3-diaminopropionate (500 mg, 1.03 mmol) was dissolved in 20 mL methanol and methanesulfonic acid (0.335 mL, 5 mmol) was added. The solution was allowed to stand at room temperature overnight and the solvent was removed by concentration. The residue was taken up in 20 mL methanol and the solution was allowed to stand at room temperature overnight. The solvent was removed by concentration and the residue was triturated with 8 mL 2-propanol. The solid product was isolated by filtration and dissolved in 12 mL 2-propanol by warming. After cooling to room temperature, crystalline solid formed. The mixture was allowed to stand in a refrigerator overnight. The crystal was filtered, washed with cold 2-propanol and dried. Yield 230 mg (41%). ES-MS (M+1): calcd 448.3; found 448.3. Analysis for $C_{22}H_{33}N_5O_9S$: calcd C 48.61, H 6.13, N 12.88; found C 48.38, H 5.91, N12.65.

Example 278b

N^2-n-butyloxycarbonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(R)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

To a solution of methyl N^2-n-butyloxycarbonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(R)-ylacetyl]-(S)-2,3-diaminopropionate hydrochloride salt (600 mg, 1.24 mmol) in 20 mL MeOH and 20 mL water cooled in an ice bath was added 1 N LiOH (1.3 mL, 1.3 mmol) over 5 min and the solution was stirred at room temperature for 5 hours. The solvents were removed by concentration at 25 °C. The

residue was taken up in 3 mL water, 3 mL acetonitrile, and 0.2 mL TFA. Purification by reversed phase HPLC gave 610 mg (89%) product. ES-MS (M+1): calcd 434.3; found 434.3.

Example 298

N^2-*n*-Butanesulfonyl-N^3-[3-(4-amidino-phenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Prepared according to Example 490a. MS (ESI, e/z, relative intensity): 454 $(M + H)^+$, (100%).

Example 299

N^2-Phenylsulfonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Prepared according to Example 490a. MS (ESI, e/z, relative intensity): 474 $(M + H)^+$, (100%).

Example 317

N^2-(2-Phenylethylsulfonyl)-N^3-[3-(4-amidino-phenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Prepared according to Example 490a. MS (ESI, e/z, relative intensity): 502 $(M + H)^+$, (100%).

Example 445a

N^2-(β-Styrylsulfonyl)-N^3-[3-(4-amidino-phenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Prepared according to Example 490a. MS (ESI, e/z, relative intensity): 500 $(M + H)^+$, (100%).

Example 478a

N^2-2,4,6-trimethylphenylsulfonyl-N^3-[3-(4-amidinophenyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

^1H NMR (DMSO-d_6) δ: 9.37 (s, 2H), 9.06 (s,2H), 8.10 (q,J=6.22 Hz, 1H), 7.98(d,J=9.52 Hz, 1H), 7.87

(s,4H),6.98 (d, J=4.40 Hz, 2H), 4.99(m,1H), 3.85 (m, 1H), 3.59-3.0 (m, 4H), 2.55 (s, 6H), 2.41 (m,2H), 2.23 (s, 3H) ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 516.3 (100)%, High Res Mass Spectrum $(M+H)^+$ calculated 516.190344, found 516.189999.sd088

Example 479a

N^2-2-chlorophenylsulfonyl-N^3-[3-(4-amidinophenyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid

M.P. 138-140°C ^{1}H NMR (DMSO-d_6) δ: 9.39 (s, 2H), 9.27 (s, 2H) 8.30 (dd, J=4.40, 9.15 Hz 1H), 8.22 (m,1H), 7.96 (d, J=6.95 Hz, 1H), 7.88 (s, 4H), 7.65 (m,2H), 7.59 (m 1H), 5.04 (m, 1H), 4.03 (m 1H), 3.58 (m 1H), 3.38 (m, 1H), 3.24 (m, 2H), 2.59 (dd,j=6.22, 14.28 Hz, 1H), 2.43 (m,1H)ppm.Mass Spectrum (ESI) m/z $(M+H)^+$ 508.1 (100%) , High Res Mass Spectrum $(M+H)^+$ calculated 508.107096, found 508.106929. sd089

Example 485a

N^α-2,3,5,6-tetramethylphenylsulfonyl-N^3-[3-(4-amidinophenyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

M.P.148-150 °C, ^{1}H NMR (DMSO-d_6) δ: 9.38 (s, 2H), 9.29 (s,2H), 8.09 (m, 1H), 7.97 (dd,J=4.40,9.15 Hz, 1H), 7.85 (s, 4H), 7.15 (d, J=7.32Hz, 1H), 4.98 (m, 1H), 3.88 (q,J=6.96, 15.75 Hz,1H), 3.56 (m, 1H), 3.34-3.08 (m, 4H), 2.43 (s,6H), 2.39 (m, 1H), 2.19 (s,3H), 2.18 (s, 3H) ppm. Mass Spectrum (ESI) m/z $(M+H)^+$ 530.2 (100%); High Res Mass Spectrum $(M+H)^+$ calculated 530.208668; found 530.208357. sd090

Example 490a

N^2-*n*-Propanesulfonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Part A: Methyl N^2-*n*-Propanesulfonyl-N^3-Boc-(*S*)-2,3-diaminopropionate

To a solution of methyl N^3-Boc-(*S*)-2,3-diaminopropionate (prepared in Ex 20, Part C, 410 mg, 1.88 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added propanesulfonyl chloride (0.21 mL, 1.9 mmol) and Et_3N (0.35 mL, 2.5 mmol) and the resulting mixture allowed to warm to room temperature overnight (18 h). The mixture was washed with 0.1 *M* HCl, sat. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give 530 mg (87%) of the desired sulfonamide as a viscous oil; CIMS (e/z, relative intensity): 342 $(M + H)^+$, 100%.

Part B: Methyl N^2-*n*-Propanesulfonyl-(*S*)-2,3-diaminopropionate Hydrochloride Salt

To neat methyl N^2-*n*-propanesulfonyl-N^3-Boc-(*S*)-2,3-diaminopropionate (520 mg, 1.60 mmol) was added 4 *M* HCl/dioxane (5 mL, 20 mmol). The resulting solution was stirred at room temperature for 4 h, then it was concentrated *in vacuo*, giving an oil. Trituration with ether (3 x 10 mL) followed by drying under vacuum afforded 383 mg (92%) of the desired amine; CIMS (e/z, relative intensity): 225 $(M + H)^+$, 100%.

Part C: Methyl N^2-*n*-propanesulfonyl-N^3[3-(4-(*N*-*t*-butoxycarbonylamidino)phenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate

To a suspension of 3-(4-*N*-Boc-amidinophenyl)isoxazolin-5-ylacetic acid (prepared in Example 32, 252 mg, 0.725 mmol), methyl N^2-*n*-propanesulfonyl-(*S*)-2,3-diaminopropionate hydrochloride (189 mg, 0.726 mmol) in DMF (5 mL) was added Et_3N (0.30 mL, 2.2 mmol) and TBTU (233 mg, 0.726 mmol). The resulting mixture was stirred for 4 h at room temperature, then was diluted with EtOAc (30 mL). It was washed with water (4 x 20 mL), sat. $NaHCO_3$ (30 mL), sat. NaCl and

dried ($MgSO_4$). Concentration *in vacuo* followed by placing the material under vacuum until constant weight was achieved afforded 292 mg (73%) of the desired amide; MS (ESI, e/z, relative intensity): 554 $(M + H)^+$, 100%.

Part D: Methyl N^2-*n*-Propanesulfonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate TFA Salt

To a solution of methyl N^2-*n*-propanesulfonyl-N^3[3-(4-(*N*-*t*-butoxycarbonylamidino)phenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate (284 mg, 0.513 mmol) in CH_2Cl_2 (4 mL) was added TFA (2 mL, 26 mmol). After 2 h at room temperature, the solution was concentrated *in vacuo* and the residue triturated with ether (3 x 5 mL). The resulting white powder was then placed under vacuum until constant weight was achieved, giving 260 mg (89%) of the desired benzamidine; MS (ESI, e/z, relative intensity): 454 $(M + H)^+$, 100%.

Part E: N^2-*n*-Propanesulfonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

To a solution of methyl N^2-*n*-propanesulfonyl-N^3[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate (100 mg, 0.176 mmol) in MeOH (1 mL) was added 0.5 *M* LiOH (0.5 mL, 0.25 mmol) and the reaction stirred at room temperature overnight (18 h). The resulting mixture was concentrated *in vacuo*, redissolved in water and the pH adjusted to 4 using 1 *M* HCl. Purification on reversed phase HPLC gave 10 mg (10%) of the desired carboxylic acid; MS (ESI, e/z, relative intensity): 440 $(M + H)^+$, (100%).

Example 492a

N^2-p-isopropylphenylsulfonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (DMSO) δ: 9.37(1H, s), 9.09(1H, s), 8.15(2H, m), 8.78(4H, d, J=1.465Hz), 7.09(2H, d, J=8.423Hz), 7.44(2H, m), 4.98(1H,m), 3.93(1H, m), 3.59(2H, m), 3.50(2H, m), 3.22(2H, m), 2.98(1H, m), 2.45(2H, m), 1.22(6H, m)ppm; ESI mass spectrum 516.3 $(M+H, 100)^+$ free base.

Example 512

Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(4-amidino-2-fluorophenyl)isoxazolin-5-ylacetyl]-*S*-2,3-diaminopropionate hydrochloric acid salt

Part A: 3-Fluoro-4-methylbenzamide

3-Fluoro-4-methylbenzoic acid (10 g, 65 mmol) was boiled in thionyl chloride (100 mL) under a drying tube for 2.5 h. The excess $SOCl_2$ was removed by distillation. The oily acid chloride product was diluted with CH_2Cl_2 (100 mL) and cooled in an ice bath. Conc. aq. NH_3 (20 mL) was added dropwise, and stirring continued at 0 °C for 0.5 h. The CH_2Cl_2 was removed *in vacuo*, then the residue was diluted with EtOAc. The mixture was extracted with sat. aq. Na_2CO_3 (2x), H_2O, and brine, dried ($MgSO_4$), and concentrated to yield 9.9 g of a pale yellow solid; mp 161-163 °C; IR(KBr) 3382, 1654 cm^{-1}; Anal. Calc. for C_8H_8FNO: C, 62.74; H, 5.27; N, 9.15; F, 12.40. Found: C, 62.66; H, 5.17; N, 9.12; F, 12.28.

Part B: 3-Fluoro-4-methylbenzonitrile

A solution of trichloroacetyl chloride (7.3 mL, 65 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 0.5 h to a solution/suspension of the Part A amide (9.0 g, 59 mmol) and Et_3N (17 mL, 120 mmol) in CH_2Cl_2 (80 mL) at 0 °C. After 40 min, the mixture was concentrated *in vacuo*, then diluted with Et_2O. This solution was extracted with 1 M

HCl, sat. aq. $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$), and concentrated to yield 7.8 g of a tan solid; mp 45-47 °C; IR(KBr) 2232 cm^{-1}; HRMS, e/z Calc. for $(M+H)^+$: 135.0484. Found: 135.0482.

Part C: <u>2-Fluoro-4-cyanobenzylbromide</u>

N-Bromosuccinimide (9.6 g, 54 mmol) and the part B substrate (7.3 g, 54 mmol) were heated under reflux in CCl_4 (100 mL) under N_2 with irradiation with a high intensity visible lamp for 2 h. After cooling to ambient temp., the mixture was filtered through a Celite pad and concentrated *in vacuo*. The crude product was recrystallized from hot cyclohexane (4x) to yield 4.5 g of off-white needles; mp 75-77 °C; IR(KBr) 2236 cm^{-1}; HRMS, e/z Calc. for $(M+H)^+$: 213.9668. Found: 213.9660.

Part D: <u>2-Fluoro-4-cyanobenzaldehyde</u>

The part C benzyl bromide (3.68 g, 17 mmol), trimethylamine N-oxide dihydrate (7.6 g, 68 mmol), CH_2Cl_2 (15 mL), and DMSO (30 mL) were stirred at 0 °C for a few h, slowly warming to ambient T overnight. The mixture was diluted with water (30 mL) and brine (30 mL), and extracted with Et_2O (4x). The combined organics were washed with brine, dried ($MgSO_4$), and concentrated to yield 1.1 g of a yellow solid; IR(KBr) 2238, 1706 cm^{-1}; HRMS, e/z Calc. for $(M+H)^+$: 150.0355. Found: 150.0341.

Part E: <u>2-Fluoro-4-cyanobenzaldoxime</u>

The part D aldehyde (1.1 g, 7.4 mmol), hydroxylamine hydrochloride (1.0 g, 15 mmol), K_2CO_3 (1.0 g, 7.4 mmol), water (1 mL), and MeOH (10 mL) were heated under reflux for 2.25 h. After brief cooling, the mixture was diluted with water, and the insoluble product was collected by filtration, then rinsed with more water. Drying under high vacuum provided 0.94 g of a pale yellow amorphous

solid; mp 179-182 °C; IR(KBr) 3256, 2236, 1556 cm^{-1}; HRMS, e/z Calc. for $(M+H)^+$: 165.0464. Found: 165.0455.

Part F: Methyl 3-(4-cyano-2-fluorophenyl)isoxazolin-5-ylacetate

The part E oxime was allowed to react with Clorox and methyl vinylacetate in the usual way to afford the isoxazoline as a yellow solid in 32% yield; mp 92-94 °C; IR(KBr) 2240, 1746 cm^{-1}; HRMS, e/z Calc. for $(M+H)^+$: 263.0832. Found: 263.0818. Anal. Calc. for $C_{13}H_{11}FN_2O_3$: C, 59.54; H, 4.23; N, 10.68; F, 7.24. Found: C, 59.84; H, 4.31; N, 10.53; F, 7.26.

Part G: Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(4-*tert*-butyloxycarbonylamidino-2-fluorophenyl)isoxazolin-(*R,S*)-5-ylacetyl-(*S*)-2,3-diaminopropionate.

The part F intermediate was converted to the title compound by the usual sequence of steps: Pinner amidine synthesis, amidine BOC protection, ester saponification, and condensation with the 2,3-diaminopropionate sulfonamide ester; MS (DCI, NH_3) 620 (M+H), 520.

Part H: Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(4-amidino-2-fluorophenyl)isoxazolin-(*R,S*)-5-ylacetyl-(*S*)-2,3-diaminopropionate hydrochloric acid salt.

The BOC group was removed from the part G intermediate by treatment with 4M HCl in dioxane to provide a yellow gum; HRMS, e/z Calc. for $(M+H)^+$: 520.1666. Found: 520.1675.

Example 512A

N^2-(*m*-Toluenesulfonyl)-N^3-[3-(4-amidino-2-fluorophenyl)isoxazolin-(*R*)-5-ylacetyl-(*S*)-2,3-diaminopropionate hydrochloric acid salt

Part A: N^2-(*m*-Toluenesulfonyl)-N^3-[3-(4-*tert*-butyloxycarbonylamidino-2-fluorophenyl)isoxazolin-(*R,S*)-5-ylacetyl-(*S*)-2,3-diaminopropionate.

The intermediate from Example 512, Part G (0.60 g, 0.97 mmol) was saponified using lithium hydroxide hydrate (61 mg, 1.45 mmol) in water (1 mL) and methanol (1 mL) at room temperature for 3 d. The mixture was extracted with ethyl acetate, the aqueous layer was acidified with pH 4 buffer, and it was extracted with ethyl acetate. The extracts were dried and concentrated to 0.427 g of a clear glass. This material was flashed chromatographed using a methanol/chloroform gradient solvent system, starting with chloroform and progressing through 2%, 10%, 15%, and 20% methanol/chloroform to give 0.360 g (57 %) of a clear glass. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.09 (br, 1H), 7.88-7.80 (m, 3H), 7.60-7.56 (m, 2H), 7.47-7.42 (m, 2H), 5.00-4.97 (m, 1H), 3.62-3.57 (m, 1H), 3.29-3.16 (m, 4H), 2.58-2.43 (m, 2H), 2.37 (s, 3H), 1.45 (s, 9H). HRMS (FAB, glycerol) Calc. for $(M+H)^+$: 606.2034. Found: 606.2043.

Part B: N^2-(*m*-Toluenesulfonyl)-N^3-[3-(4-amidino-2-fluorophenyl)isoxazolin-(*R*)-5-ylacetyl-(*S*)-2,3-diaminopropionate hydrochloric acid salt.

The intermediate from Part A (0.344 g, 0.57 mmol) was dissolved in 4M HCl in dioxane and stirred at room temperature for 21.5 h. The solution was diluted with ether and the precipitated white solid was collected and dried, yielding 0.367 g. This material was subjected to super critical fluid chiral Prep HPLC on a Chiral OG 2 in x 25 cm column using 0.1% TFA, 25% methanol, 75% carbon dioxide as eluent at a flow rate of 20 mL/min to separate the isoxazoline isomers. The second eluting, (*R,S*), isomer was obtained as a white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.81 (br, 1H), 9.53 (s, 1.5H), 9.29 (s, 1.5H), 8.17 (m, 2H), 7.95 (t, J=7.7 Hz, 1H), 7.86 (d, J=12.0 Hz, 1H), 7.40 (d, J=9.5 Hz, 1H), 7.60-7.56 (m, 2H), 7.46-7.41

(m, 2H), 4.97-4.93 (m, 1H), 3.88-3.86 (m, 1H), 3.59-3.55 (m, 1H), 3.42-3.14 (m, 3H), 2.52-2.45 (m, 1H), 2.41-2.33 (m, 4H). HRMS (FAB, glycerol) Calc. for $(M+H)^+$: 506.1510. Found: 506.1494.

Example 513

Methyl N^2-(*n*-butyloxycarbonyl)-N^3-[3-(3-amidinopyrid-6-yl)isoxazolin-5-ylacetyl]-*S*-2,3-diaminopropionate hydrochloric acid salt

Prepared using methods described in Ex. 514 to provide a pale yellow powder; mp 90-110 °C (dec); HRMS, e/z Calc. for $(M+H)^+$: 449.2149. Found: 449.2140.

Example 514

Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(3-amidinopyrid-6-yl)isoxazolin-5-ylacetyl]-*S*-2,3-diaminopropionate hydrochloric acid salt

Part A: 3-cyano-6-pyridaldoxime

5-Cyano-2-picoline (25 g, 0.21 mol) and I_2 were heated under reflux in DMSO (200 mL) for 1 h. After cooling to RT, hydroxylamine hydrochloride (16 g, 0.23 mol), K_2CO_3 (29 g, 0.21 mol), and water (21 mL) were added. The resulting mixture was heated to 80 °C for 2.5 h, cooled, diluted with water (100 mL) and much acetone, and absorbed onto silica gel by concentration. Chromatography on silica gel, eluting with 0% to 50% EtOAc in hexane, afforded 12.2 g of a tan solid; mp 204-207 °C (dec); HRMS, e/z Calc. for $(M+H)^+$: 148.0511. Found: 148.0516.

Part B: Methyl 3-(3-cyanopyrid-6-yl)isoxazolin-5-ylacetate

The oxime of Ex. 514, part A was converted to the isoxazoline as described in Ex. 516, part B in 76% yield as a yellow solid; mp 97-98 °C; HRMS, e/z Calc. for

$(M+H)^+$: 246.0879. Found: 246.0881. Anal. Calc. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.74; H, 4.51; N, 17.11.

Part C: Methyl 3-(3-*t*-butyloxycarbonylamidinopyrid-6-yl)isoxazolin-5-ylacetate

The nitrile of Ex. 514, part B was converted to the amidine as described in the method of Ex. 516, parts D & E (except that 0.6 eq. NaOMe was required), and BOC protected in standard fashion to afford, after purification, a yellow solid; mp 143 °C (gas evolves); HRMS, e/z Calc. for $(M+H)^+$: 363.1668. Found: 363.1675. Anal. Calc. for $C_{17}H_{22}N_4O_5$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.35; H, 6.10; N, 15.39.

Part D: Lithium 3-(3-*t*-butyloxycarbonylamidinopyrid-6-yl)isoxazolin-5-ylacetate

The ester of Ex. 514, part C was saponified and lyophilized as described in the method of Ex. 516, part F to give a colorless amorphous solid quantitatively; mp >230 °C; HRMS, e/z Calc. for conjugate acid $(M+H)^+$: 349.1512. Found: 349.1527.

Part E: Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(3-*tert*-butyloxycarbonylamidinopyrid-6-yl)isoxazolin-(*R,S*)-5-ylacetyl]-(*S*)-2,3-diaminopropionate.

The Part D lithium carboxylate was condensed with methyl N^2-(*m*-toluenesulfonyl)-(*S*)-2,3-diaminopropionate hydrochloride using conditions described above to give a yellow foam. HRMS, e/z Calc for $(M+H)^+$: 603.2237. Found: 603.2223.

Part F: Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(3-amidinopyrid-6-yl)isoxazolin-(*R,S*)-5-ylacetyl]-(*S*)-2,3-diaminopropionate hydrochloric acid salt.

The protected amidine of Part E was treated with 4M HCl in dioxane to provide a yellow solid; mp 90°C (dec); HRMS, e/z Calc. for $(M+H)^+$: 503.1713. Found: 503.1718.

Example 514A

N^2-(*m*-Toluenesulfonyl)-N^3-[3-(3-amidinopyrid-6-yl)isoxazolin-(*R*)-5-ylacetyl]-(*S*)-2,3-diaminopropionic acid trifluoroacetic acid salt

Part A: Lithium N^2-(*m*-toluenesulfonyl)-N^3-[3-(3-*tert*-butyloxycarbonylamidinopyrid-6-yl)isoxazolin-(*R,S*)-5-ylacetyl]-(*S*)-2,3-diaminopropionate.

The methyl ester of Example 514, Part E (0.16 g, 0.27 mmol) was saponified by stirring with 0.5 M LiOH (0.54 mL, 0.27 mmol) in methanol (2 mL) at room temperature. The mixture was concentrated *in vacuo* to give 0.16 g (99 %) of a tan solid; HRMS, e/z Calc for $(M+H)^+$: 589.2081. Found: 589.2086.

Part B: N^2-(*m*-Toluenesulfonyl)-N^3-[3-(3-amidinopyrid-6-yl)isoxazolin-(*R*)-5-ylacetyl]-(*S*)-2,3-diaminopropionic acid trifluoroacetic acid salt.

The lithium salt of Part A was treated with 4M HCl in dioxane to give a tan foam. This material was purified by Prep reverse phase HPLC on a Vydac C18 2 x 25 cm column using a gradient solvent system starting with 0.05% TFA in water progressing to 80:20 0.05% TFA in water: 0.05% TFA in acetonitrile over 50 m, the purified material was subjected to super critical fluid Prep chiral HPLC on a Chiral OG 2 in x 25 cm column using 0.1% TFA, 25% methanol, 75% carbon dioxide as elutant at a flow rate of 20 mL/min to separate the isoxazoline isomers. The second eluting, (*R,S*), isomer was resubmitted to reverse phase Prep HPLC as above to give the title compound as a tan solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 2.31 (dd, J=15.0, 7.0 Hz, 1H, partially obscured), 2.37 (s, 3H), 2.48-2.59 (m,

1H, under DMSO), 3.02-3.15 (m, 1H), 3.22 (dd, J=17.6, 10.6 Hz, 1H), 3.32-3.42 (m, 1H, under water peak), 3.55 (dd, J=17.6, 10.6 Hz, 1H), 3.82-3.92 (m, 1H), 4.98-5.11 (m, 1H), 7.39-7.49 (m, 2H), 7.54-7.61 (m, 2H), 8.08-8.15 (m, 3H), 8.25 (dd, J=8.4, 2.2 Hz, 1H), 9.01 (d, J=1.8 Hz, 1H), 9.24 (br s, 2H), 9.53 (br s, 2H), 12.78 (very br s, 1H). MS (ESI) 489 (M+H, 65), 288 (100), 245 (27).

Example 515

Methyl N^2-(*n*-butyloxycarbonyl)-N^3-[3-(2-amidinopyrid-5-yl)isoxazolin-5-ylacetyl]-*S*-2,3-diaminopropionate hydrochloric acid salt

In similar fashion to the method described in Ex. 516, the compound of Ex. 514, part E was coupled with methyl N^2-(*n*-butyloxycarbonyl)-2,3-diaminopropionate hydrochloride using conditions described above, followed by BOC deprotection with 4 M HCl/dioxane to yield a pale yellow powder; HRMS, e/z Calc. for $(M+H)^+$: 449.2149. Found: 449.2154.

Example 516

Methyl N^2-(*m*-toluenesulfonyl)-N^3-[3-(2-amidinopyrid-5-yl)isoxazolin-5-ylacetyl]-*S*-2,3-diaminopropionate hydrochloric acid salt

Part A: 2-Chloro-5-pyridaldoxime

2-Chloro-5-formylpyridine (2.1 g, 15 mmol) was condensed with hydroxylamine hydrochloride in the usual way to give the oxime, 1.5 g, as a yellow crystalline solid; mp 171-175 °C (dec); HRMS, e/z Calc. for $(M+H)^+$: 157.0169. Found: 157.0175.

Part B: Methyl 3-(2-chloropyrid-5-yl)isoxazolin-5-ylacetate

Sodium hypochlorite (5% wt, 20 mL) was added dropwise over 1.75 h to a mixture of the part A oxime (1.13 g, 7.2 mmol), methyl vinylacetate (70% purity, 3.0 g, 21 mmol),

= 14.6, 6.6 Hz, 1H), 2.54 (s, 3H), 2.38 (dd, J = 14.6, 7.3 Hz, 1H), 2.33 (s, 3H, MsOH); MS (ESI): *m/e* 493.2 $(M+H)^+$; Anal. Calcd. for $C_{21}H_{28}N_6O_{10}S_2$: C, 42.85; H, 4.79; N, 14.05; S, 10.89. Found: C, 42.45; H, 4.74; N, 14.05; S, 11.19.

Example 2420

Methyl N^2-n-butyloxycarbonyl-N^3-[3-(4-piperidinylpropyl)isoxazolin-5-(R,S)-ylformyl)-(S)-2,3-diaminopropionate TFA salt,sc568

^{1}HNMR ($CDCl_3$) δ 7.38(1H, brd), 6.95(1H,brd), 5.65(1H, m), 4.98(1H, m), 4,42(1H, m),4.06(2H, m), 3.76(3H, s), 3.65(2H, m), 3.48(2H, m), 3.25(2H, m), 2.95(2H, m), 2.4(2H, m), 1.95(2H, brd), 1.6(5H, m), 1.48(2H, m), 1.35(4H, m), 0.94(3H, m)ppm; ESI mass spectrum 441 $(M+H)^+$ free base

Example 2421

Methyl N^2-p-toluenesulfonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5-(R,S)-ylformyl]-(S)-2,3-diaminopropionate TFA salt,sc570

^{1}HNMR ($CDCl_3$) δ: 7.8(1H, m), 7.68(2H, m), 7.3(3H, m), 5.7(1H, m),4.92(1H, m), 4.1(1H, m), 4.0(1H, m), 3.7(2H, m), 3.55(3H, s), 3.45(3H, m), 2.9(2H, brd), 2.4(3H, s), 2.38(2H, m), 1.9(3H, m), 1.65(2H, m), 1.54(2H, m), 1.35(2H, m)ppm; ESI mass spectrum 495.3 $(M+H)^+$ free base.

Example 2422

N^2-p-toluenesulfonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5-(R,S)-ylformyl]-(S)-2,3-diaminopropionic acid TFA salt,sc571

^{1}HNMR (CD_3OD)δ: 7.7(2H, m), 7.32(2H, m), 4.85(1H, m), 4.1(1H, m), 3.75(1H, m), 3.65(2H, m), 3.32(3H, m), 3.2(2H, m), 2.9(2H, m), 2.4(5H, m), 1.95(2H, m), 1.62(3H, m), 1.35(4H, m),ppm; ESI mass spectrum 481.3 $(M+H)^+$ free base

Part B to give 25.0 mg (75 %) of a white solid. mp 158.5-161.5°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.31-2.44 (m, 1H), 2.37, 2.38 (singlets, 3H), 2.50-2.60 (m, 1H, under DMSO), 3.00-3.10 (m, 0.5H), 3.12-3.36 (m, 2H), 3.38-3.48 (m, 0.5H), 3.60 (ddd, J=17.2, 10.6, 5.9 Hz, 1H), 3.85-3.95 (m, 1H), 4.95-5.11 (m, 1H), 7.39-7.45 (m, 2H), 7.52-7.60 (m, 2H), 8.10-8.22 (m, 2H), 8.28-8.40 (m, 2H), 9.06 (s, 1H), 9.37 (br s, 2H), 9.60 (br s, 2H). MS (ESI) 489 (M+H, free base, 100), 214 (17).

Example 528a

N^2-o-Bromophenylcarbonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid.

The title compound was obtained as its TFA salt from readily accessible N^2-amino-3-[(4-tertbutyloxycarbonylamidino)phenylisoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diamino-tertbutylpropionate by common acylation techniques with 2-bromobenzoyl chloride. Removal of the tert-butyl protecting groups with TFA afforded the desired product as colorless crystals. M.P. 172-174°C; ^{1}H NMR (DMSO d_6) δ: 7.80(d, J=8Hz,2H), 7.51-7.63(m,3H), 7.28(m,2H), 7.12(dd,1H), 6.61(m,1H), 5.05(m,1H), 4.81(q, 1H), 3.80(d, 3H), 3.06(m,1H), 2.53(m,2H), 1.53(s, 9H)ppm; ESI mass spectrum 516(M+H, 100 free base); HRMS calcd. for $C_{22}H_{23}BrN_5O_5$ 516.088255, found 516.086811(free base).se729

Example 536

N^2-(2,5-Dimethyl-4-chlorobenzenesulfonyl)-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Prepared according to Example 490a. MS (ESI, e/z, relative intensity): 536 (M + H)$^+$, (100%).

Example 540

N^2-methylphenylcarbonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid.

Obtained as colorless crystals, M.P. 166-168°C; ^{1}H NMR (DMSO d_6) δ: 9.38(b, 2H), 9.18(b,2H), 8.42(t,1H), 8.20(m,1H), 7.21(d, J=10.2Hz, 4H), 5.00(m, 1H), 4.50(m,1H), 3.30-3.73(m.3H), 2.58-2.65(dd,1H), 2.41-2.50(dd, 1H), 2.34(s,3H)ppm; ESI mass spectrum 452(M+H, 100 free base); HRMS calcd for $C_{23}H_{26}N_5O_5$ 452.193394, found 452.1922251(free base).se728

Example 540a

N^2-methylphenylsulfonyl-N^3-[3-(4-amidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid.

Obtained as colorless crystals M.P. 136-138°C; ^{1}H NMR (DMSO d_6) δ: 9.39(b, 2H), 9.27(s,2H), 8.18(m,2H), 7.80(d, J=7.7Hz,1H), 7.44(t,1H), 7.32(q,2H), 4.96(m,1H), 3.90(b, 1H), 3.81(q, 1H), 3.40-3.60(m,2H), 3.04(m,2H), 2.60(s,2H), 2.24(dd, J=7.7 and 15.6Hz)ppm; ESI mass spectrum 488(M+H, 100 free base). HRMS calcd for. $C_{22}H_{25}N_5SO_6$ 488.160381, found 488.16292 (free base).

Example 606

Methyl N^2-p-toluylsulfonyl-N^3-[3-(4-guanidinophenyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA Salt

Part A: The methyl di-Boc-quanidino-α-toluyl ester was prepared according to the procedure for example 602. Deprotection of the Boc-protecting groups then afforded example 606 as the TFA salt. ^{1}HNMR (DMSO) δ: 8.30(dd, 2H), 8.09(m, 1H), 7.68(d, J=8.2Hz, 2H), 7.60(d, J=8.0Hz, 2H), 7.35(d, J=8.2Hz, 2H), 7.28(d, J=8.4Hz, 2H), 4.88(m, 1H), 4.00(m, 1H), 3.42(dt, 1H), 3.38((d, 3H), 3.05-3.33(m, 3H), 2.40(m, 1H), 2.36(s, 3H), 2.25(m,1H)ppm; HR MS calcd. for $C_{23}H_{29}N_6O_6S$ 517.186930; Found 517.186911. sa710

Part B: Lithium hydroxide saponification on the product of part A then afforded example 605 in 39% yield after recrystallization from dichloromethane and ether. 1HNMR (CD_3OD) δ: 8.29(brd, S, 2H), 8.05(brd, s, 1H), 7.75(d, J=8.1Hz, 2H), 7.70(d, J=8.4Hz, 2H), 7.31(d, 4H), 5.02(m, 1H), 3.85(m, 1H), 3.60(m, 2H), 3.41(m, 1H), 3.20(m, 1H), 2.64(dd, 1H), 2.43(dd, 1H), 2.40(s, 3H);HR MS calcd. for $C_{22}H_{27}N_6O_6S$ 503.171280; Found 503.170531. sa760

Example 625

N^2-p-methylphenylsulfonyl-N^3-[3-(4-amidinophenylmethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

Part A: 1-β-nitroethene-4-benzonitrile (Bourgvignon, J.et al., Can, J. Chem., 1985, 63, 2354) (0.9 g, 5.17 mmol) was reduced according to the method of Nakamura, et al. (Chem. Lett.,1985, 523) to afford 0.73 g (80%) of desired product. ^1H NMR ($CDCl_3$) δ: 7.73 (d, J=8.42 Hz, 2H), 7.43 (d, J=8.42 Hz, 2H), 4.75 (d, J=6.96 Hz, 2H), 3.48 (d, J=6.96 Hz, 2H) ppm; Mass Spectrum (CH_4-CI) m/z $(M+H)^+$ 177 (100%).

Part B: 1-β-nitroethane-4-benzonitrile (1.38 g, 7.8 mmol) was condensed with tert-butyl acrylate (1.4 ml, 9.4 mmol) according to the method of Curran, D.P., et al (J. Org. Chem., 1988, 53, 5369) to afford the crude ester. The ester was difficult to purify so the ester was hydrolyzed in 30 ml of 30% TFA/CH_2Cl_2 for 48h. The crude acid was extracted into aqueous $NaHCO_3$. The aqueous layer was acidified and extracted with CH_2Cl_2 and dried ($MgSO_4$) to afford 1.48 g (80%) orange solid.^1H NMR ($CDCl_3$) δ: 7.97 (brd, 1H), 7.64 (d, J=8.42 Hz, 2H), 7.36 (d, J=8.42 Hz, 2H), 5.07 (dd, J=6.59,10.98 Hz, 1H), 3.79 (s, 2H), 3.20 (m, 2H) ppm.

Part C: The product of Part B (366 mg, 1.6 mmol) was coupled with methyl-L-N^{α}-p-toluylsulfonyl-2,3-diaminoproprionate using procedure described in Example

43D. Chromatography on silica gel (2%MeOH/CH_2Cl_2) afforded 388 mg (50%).mp 141-144^oC; ^1H NMR ($CDCl_3$) δ: 7.75-7.65 (m, 2H), 7.60 (d, 2H), 7.45 (d, 2H), 7.30 (dd, 2H), 7.20 (m, 1H), 5.50 (dd, 1H), 4.99 (m, 1H), 4.20-3.99 (m, 1H), 3.90-3.70 (m, 3H), 3.55 (s, 3H), 3.30 (m, 3H), 2.42 (s, 3H)ppm; Mass Spectrum (NH_3-CI) m/z $(M+H)^+$ 485.2 (100%); IR (KBr) 3276, 1738, 1666, 1538, 1338, 1162, 862, 822 cm^{-1}.

Part D: The product of Part C (360 mg, 0.74 mmol) was subjected to the Pinner reaction previously described. Chromatography on silica gel (5-15% MeOH/CH_2Cl_2) afforded 313 mg (75%).mp 133-137^oC; ^1H NMR (DMSO-d_6) δ: 9.20 (brd, 2H), 8.26 (t, J=5.86 Hz, 1H), 7.80 (d, J=8.06 Hz, 2H), 7.63 (d, J=8.06 Hz, 2H), 7.51 (d, J= 8.06 Hz, 2H), 7.38 (d, J=8.06 Hz, 2H), 4.87-4.73 (m, 1H), 3.98-3.89 (m, 1H), 3.80 (s, 2H), 3.34 (s, 3H), 3.34-3.31 (m, 3H), 3.28 (m, 2H), 2.98 (dd, J=6.23, 17.21 Hz, 1H), 2.37 (s, 3H)ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 502.2 (100%).

Part E: To the product of Part D (182 mg, 0.338 mmol) was added 1 ml MeOH, followed by lithium hydroxide (31 mg, 0.74 mmol). The mix ture was stirred for 18h and the solvent was removed *in vacuo* and water added. HCl was added until a precipitate formed. The solid was filtered off and stirred in 2 ml HCl for 1 h. The acid was removed *in vacuo* to afford 72 mg of product which contained 15% methyl ester. Purification via standard HPLC techniques then afforded the desire product. ^1H NMR (DMSO -d_6) δ: 9.35 (s, 2H), 9.08 (s, 2H), 8.14-8.07 (m, 2H), 7.78 (d, J=7.32 Hz, 2H), 7.66 (dd, J= 2.19, 8.42 Hz, 2H), 7.51 (d, J=7.69 Hz, 2H), 7.36 (d, J=8.42 Hz, 2H), 4.86-4.69 (m, 1H), 3.92-3.80 (m, 1H), 3.79 (s, 2H), 3.30-2.90 (m, 4H), 2.49 (s, 3H)ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 488.3 (100%).

Example 666

N^2-(methyl)-N^2-m-toluylsulfonyl-N^3-[3-(4-amidinophenyl)-isoxazoline-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

Part A: Methyl N^3-[3-(4-cyanophenyl)isoxazolin-5-(R,S)-ylacetyl]-N^2-m-toluyl-(S)-2,3-diaminopropionate obtained as the precursor to Example 300 was subjected to a selective Mitsonubo-N-methylation of the sulfonamide (Acta. chem. scand. 1994,48,324333),to afford methyl N^2-(methyl)-N^2-m-toluyl-N^3-[3-(4-cyanophenyl)isoaxzolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionate as colorless crystals. M.P=148-149^{0}C. ^{1}HNMR($CDCl_3$) δ: 7.77(d, 2H), 7.60(m, 2H), 7.46(m, 2H), 7.41(d, 2H), 6.07(t, 1H), 5.21(m, 1H), 4.80(dd,J=4.8&10.6Hz, 1H), 3.81(m, 1H), 3.56(s, 3H), 3.43(m, 2H), 3.25(dd,J=7.4&17.4Hz, 1H), 2.80(dd,J=8&17.1Hz,1H), 2.77(s, 3H), 2.56(dd, J=7.7&15.1Hz,1H), 2.44(s, 1H)ppm; IR (KBr) 3340, 2224, 1726, 1644, 1610, 1596, 1534, 1440, 1414, 1402, 1366, 1336, 1284, 1258, 1212, 1144, 1012, 934, 918, 896, 844, 812, 784, 690, cm^{-1}. ESI mass spectrum 499 (M+H,48), 359(63), 279(53), 198(100). HR MS calcd. for $C_{24}H_{27}N_4O_6S$ 499.165132 found 499.164946. sd267

Part B: The cyano procursor from part A was then subjected to the Pinner amidine reaction conditions as per example 275E to obtain the desired compound as the methyl ester sc758in 60% overall yield. Saponification with 6N HCl followed by HPLC purification [solvent A: CH_3CN: H_2O: TFA / 2%: 98%:0.05%, solvent B: CH_3CN:H_2O:TFA / 80%:20%:0.05%] afforded the desired amidine acid compound 666 as its TFAsalt. ^{1}HNMR ($CDCl_3$) δ: 9.35(s, 1H), 9.23(s,1H), 8.20(brd, 2H), 7.89(brd, 4H), 7.57(d,J=8Hz, 2H), 7.40(d,J=8Hz, 2H), 5.05(m, 1H), 4.67(m, 1H), 3.50-3.66(m, 3H), 3.20-3.40(m, 2H), 2.80(s, 3H), 2.55(m, 1H), 2.35(m/s, 4H)ppm; ESI mass spectrum 502(M+H, 100), HRMS calcd for $C_{23}H_{27}N_5SO_6$ 502.176031 found 502.176612.

Example 717

N^2-Phenylmethylsulfonyl-*N*^{3}-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

Prepared according to Example 490a. MS (ESI, e/z, relative intensity): 488 $(M + H)^+$, (100%).

Example 816

N2-p-toluylsulfonyl-N3-[5-(4-amidinophenyl)isoxazolin-3-(R,S)-yl-acetyl]-(S)-2,3-diaminopropionic acid TFA salt.

The title compound was prepared in a manner similar to example 829. Saponification of the methyl ester via standard techniques then afforded crude compound 816, which was purified via HPLC [graduant flow, solvent A CH_3CN(2%) : H_2O(98%) : TFA(0.05%), solvent B: CH_3CN(80%) : H_2O(20%) : TFA(0.05%),] to afford colorless crystals of compound 816 as its TFA salt. ^{1}HNMR($CDCl_3$) δ: 9.30(brds, 4H), 8.34(t, 1H), 8.12(d,J=9.2Hz, 1H), 7.81(d, J=8.3Hz, 1H), 7.60(d, J=8.0Hz, 1H), 5.60(dt, 1H), 3.81(q, 1H), 3.43(dt, 1H), 3.25(m, 1H), 3.20(d, 1H), 3.03(m, 1H), 2.89(m, 1H), 2.50(s, 1H), 2.34(s,3H)ppm; ESI mass spectrum 488(M+H,100), HRMS calcd. for $C_{22}H_{26}N_5O_6S$ 488.160381; found 488.158785.

Example 952

Methyl N2-m-toluenesulfono-N3-[3-(4-N-isopropylamidophenyl)isoxazolin-5R-ylacetyl]-S-2,3-diaminopropionate

Methyl N^2-m-toluenesulfono-N^3-[3-(4-cyanophenyl)isoxazolin-5R-ylacetyl]-S-2,3-diaminopropionate (prepared as in example 473 part C above) (0.098g, 0.0002mol) was stirred with isopropyl alcohol (0.018ml, 0.0002mol) and sulfuric acid (5ml) for 12 hours. The reaction mixture was poured over ice and diluted to three times its' volume with water. The title compound was filtered as a pale brown solid. ^{1}H NMR ($CDCl_3$) δ: 7.79-7.61(m, 6H); 7.38-7.36(m, 2H); 6.49-6.40(m, 1H); 6.01-5.99(m, 1H); 5.62-5.55(m, 1H); 5.19-5.08(m, 1H); 4.31-4.28(m, 1H); 4.11-3.99(m, 1H); 3.56(s, 3H); 3.72-3.48(m, 4H); 3.24-3.16(dd, 1H, J=7.3, 17.0);

2.41(s, 3H); 1.29-1.27(d, 6H, J=6.59Hz). MS(ESI) calc'd for $C_{26}H_{32}N_4SO_7$ 545.3 found 545.2 $(M+H)^+$

Example 954

N^2-3-(n-butylcarbamoyl)-N^3-[3-(4-amidophenyl)isoxazolin-5R-ylacetyl]-S-2,3-diaminopropionic acid

Following the procedure outlined for example 1945 above, Methyl N^2-3-(n-butylcarbamoyl)-N^3-[3-(4-cyanophenyl)isoxazolin-5R-ylacetyl]-S-2,3-diaminopropionate (0.87g, 0.002mol) gave a 66% yield of N^2-3-(n-butylcarbamoyl)-N^3-[3-(4-amidophenyl)isoxazolin-5R-ylacetyl]-S-2,3-diaminopropionic acid. 1H NMR (CDCl3) δ: 12.7(bs, 1H); 8.12-8.09 and 7.28-7.26(2m, 1H); 8.05 and 7.43(2s, 1H); 7.94-7.92(d, 2H, J=8.54); 7.87(s, 1H); 7.73-7.70(d, 2H, J=8.5Hz); 6.51-6.49(m, 1H); 5.02-4.95(m, 1H); 3.95-3.90(m, 1H); 3.58-3.47(m, 2H); 3.29-3.13(m, 2H); 2.72-2.38(m, 4H); 1.52-1.46(m, 2H); 1.34-1.25(m, 2H); 0.87-0.85(t, 3H, J=4.3Hz). MS(ESI): Cacl'd for C20H26N4O7 435.2 found 435.2$(M+H)^+$.

Example 956

N^2-3-methylphenylsulfonyl-N^3-[3-(4-amidophenyl)-5R-ylacetyl]-S-2,3-diaminopropionic acid

Part A: Methyl N^2-m-toluenesulfono-N^3-[3-(4-amidophenyl)-5S-ylacetyl]-S-2,3-diaminopropionate hydrochloride.

Methyl N^2-m-toluenesulfono-N^3-[3-(4-cyanophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate (0.19g, 0.00039mol) was dissolved in 10ml concentrated sulfuric acid. After stirring for 12 hours the reaction mixture was poured over 10g of ice and 20ml of water was added. The white solid was filtered, washed once with water and dried under vacuum overnight to give methyl-N^2-m-toluenesulfono-N^3-[3-(4-amidophenyl)-5S-ylacetyl]-S-2,3-diaminopropionate as a white powder. IR(neat) cm^{-1}: 3404, 3340, 3274, 3202, 2930, 1710, 1652, 1612, 1526, 1320, 1286, 1238, 1174,

1100, 1086, 1070, 886, 850, 614, 574. MS(ESI): calc'd for $C_{23}H_{26}N_4O_7S$ 503.2 found 503.3$(M+H)^+$.

Part B: N^2-m-toluenesulfono-N^3-[3-(4-amidophenyl)-5R-ylacetyl]-S-2,3-diaminopropionic acid

Methyl N^2-m-toluenesulfono-N^3-[3-(4-amidophenyl)-5R-ylacetyl]-S-2,3-diaminopropionate hydrochloride (0.146g, 0.29mmol) was dissolved in MeOH (5ml), LiOH (0.013g, 0.32mmol) in H_2O (5ml) was added and the reaction mixture left to stir overnight. Purification was done by HPLC on a Vyadek column using a gradient of 0.05%TFA/water to 0.05%TFA/acetonitrile over 45min. The flow was set to 10ml/min and the detector at 254nm. The peak eluted at 25min, the volatiles were evaporated *in vacuo*, and the solid dried under vacuum. MS(ESI) calc'd for $C_{22}H_{24}N_4O_7S$: 489.2 found: 489.2.

Example 978

Methyl N^2-m-toluenesulfono-N^3-[3-(5-amidopyrid-2-yl)isoxazolin-5S-ylacetyl]-S-2,3-diaminopropionate

mp 192-195.5°C (dec). ^1H NMR (DMSO-d_6, 300 MHz) δ 2.28 (dd, J=14.6, 7.0 Hz, 1H), 2.36 (s, 3H), 2.44-2.54 (m, 1H, under DMSO), 3.04-3.15 (m, 1H), 3.20 (dd, J=17.6, 7.3 Hz, 1H), 3.30-3.40 (m, 1H, under water), 3.53 (dd, J=17.6, 10.6 Hz, 1H), 3.80-3.89 (m, 1H), 4.92-5.05 (m, 1H), 7.38-7.48 (m, 2H), 7.54-7.61 (m, 2H), 7.68 (br s, 1H), 7.98 (d, J=8.1 Hz, 1H), 8.04-8.10 (m, 2H), 8.23 (br s, 1H), 8.27 (dd, J=8.1, 2.2 Hz, 1H), 9.06 (d, J=1.5 Hz, 1H), 12.76 (br s, 1H). IR (KBr) 3388, 3314, 3274, 3186, 1712, 1662, 1584, 1546, 1418, 1344, 1160, 934, 794, 712, 688, 620, 576 cm^{-1}. MS (ESI) 490 (M+H, 100).

Example 979

N^2-[(p-ethyl)phenylsulfonyl]-N^3-[3-(4-carboxamidophenyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionateSE101

^{1}HNMR (DMSO) δ 8.12(2H,m), 7.94(2H, d, J=8.423Hz), 7.74(2H, m), 7.70(2H, d, J=8.423Hz), 7.46(1H, s),7.40(2H, m), 4.94(1H, m), 3.92(1H, m), 3.56(2H, m), 3.37(3H, m), 2.70(2H, m), 2.45(3H, m), 1.22(3H, m)ppm; MS (ESI) m/z 503.3 $(M+H)^+$.

Example 996

N^2-o-toluenesulfonyl-N^3-[5-(4-amidinophenyl)isoxazolin-3(R,S)-ylformyl]-(S)-2,3-diaminopropionic acid TFA salt.se730

Standard cycloaddition techniques using ethylchlorooximido acetate(Aldrich) and 4-cyanostyrene agfforded the desired precursor ethyl-5-(4-cyanophenyl)-isoxazoline carboxylate. Saponification followed by coupling with methyl N^2-o-toluylsulfonyl-(S)-2,3-diaminopropionate via standard techniques afforded the desired cyanoprecursor. Formation of the amidine via standard Pinner reaction conditions afforded the desired compound as colorless crystals after HPLC purification; M.P. 84-86^{o}C; ^{1}HNMR(DMSO d_6) δ: 9.45(b, 1H), 9.35(b, 1H), 8.40(q, 1H), 8.21(dd, 1H), 7.81(t,2H), 7.77(d, J=8.5Hz, 2H), 7.55(d, J=8.5Hz, 2H), 7.38-7.49(t, 1H), 7.25(m, 2H), 5.83(m, 1H), 3.89(q, 1H), 3.23-3.71(m, 3H), 2.98(q, 1H), 2.57(s,3H)ppm; ESI mass spectrum 474 (M=H, 100 free base); HRMS calcd for $C_{21}H_{24}N_5O_6S$ 474.144731, found 474.143847.

Example 1540

2-(*n*-Butyloxycarbonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionic acid bis trifluoroacetic acid salt

Part A: 3-(4-Cyanophenyl)-8-benzyloxycarbonyl-1-oxo-2,8-diazaspiro[4.5]dec-2-ene.

The title material was prepared from 4-cyanobenzaldoxime (7.0 g, 48 mmol) and 1-benzyloxycarbonyl-4-methylenepiperidine (De Amici, M.;

Frølund, B.; Hjeds, H. Krogsgaard-Larsen, P. *Eur. J. Med. Chem.* **1991**, *26*, 625) (11.0 g, 48 mmol) as described in Example 4, Part B. The crude adduct was purified by flash chromatography using a gradient hexane/ethyl acetate solvent system, starting with hexane and progressing to 65 % ethyl acetate/hexane in 5 % increments to give 14.4 g (86 %) of a pale yellow gum. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.75 (d, J=8 Hz, 2H), 7.69 (d, J=8 Hz, 2H), 7.37-7.29 (m, 5H), 5.15 (s, 2H), 3.95-3.83 (m, 2H), 3.51-3.44 (m, 2H), 3.09 (s, 2H), 2.00-1.89 (m, 2H), 1.83-1.70 (m, 2H). IR (KBr) 2228, 1698 cm^{-1}. HRMS (DEP, NH_3) Calc. for $(M+H)^+$: 376.1661. Found: 376.1646.

Part B: <u>3-(4-Amidinophenyl)-1-oxo-2,8-diazaspiro[4,5]dec-2-ene dihydrochloric acid salt.</u>

The intermediate of Part A (4.18 g, 11.1 mmol) was subjected to standard Pinner conditions to give a crude amidine-amine salt, which was purified by flash chromatography using a graduated solvent system starting with chloroform and progressing to 30 % methanol in chloroform to give 1.8 g (48 %) of the title compound. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.56 (br s, 1.5H), 9.36 (br s, 1.5H), 7.95 (d, J=8.7 Hz, 2H), 7.86 (d, J=8.4 Hz, 2H), 4.15-4.14 (m, 1H), 3.43 (s, 2H), 3.36 (s, 4H), 2.05-2.04 (m, 4H). HRMS (DEP, NH_3) Calc. for $(M+H)^+$: 259.1559. Found: 259.1562.

Part C: <u>Methyl 2-(*R,S*)-(benyloxycarbonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionate dihydroiodic acid salt.</u>

The intermediate of Part B (1.67 g, 5.0 mmol) was dissolved in dimethylformamide (20 mL) and sodium bicarbonate (1.27 g, 15.1 mmol) was added. A solution of N-benzyloxycarbonyl-3-iodo-L-alanine methyl ester (Märki, W.; Schwyzer, R. *Helv. Chim. Acta* **1975**, *58*, 1471) (2.0 g, 5.5 mmol) in dimethylformamide (6 mL) was added and the

mixture was stirred at room temperature for 7 d. The solvent was evaporated and the residue was flash chromatographed using a graduated solvent system starting with chloroform and progressing to 20 % methanol/chloroform in 5 % steps to give 1.78 g of impure material. It was chromatographed a second time as above to give 1.72 g (45 %) of pure material. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.16 (br s, 4H), 7.87 (s, 4H), 7.71 (d, J=7.7 Hz, 1H), 7.39-7.30 (m, 5H), 5.10-5.05 (m, 2H), 4.29-4.27 (m, 1H), 3.65 (s, 3H), 3.23 (s, 2H), 2.66-2.60 (m, 4H), 2.46 (m, 2H), 1.75 (m, 4H). IR (KBr) 3300-2950 (br), 1718, 1674 cm^{-1}. HRMS (FAB, glycerol) Calc for $(M+H)^+$: 494.2403. Found: 494.2401.

Part D: <u>Methyl 2-(*R,S*)-amino-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionate trihydrobromic acid salt.</u>

The intermediate of Part C (1.2 g, 1.6 mmol) was dissolved in 30 % hydrogen bromide in acetic acid (10 mL) and the solution was stirred at room temperature for 17.5 h. The mixture was diluted with ether and filtered. The solid was washed with ether and dried to give 0.872 g (89 %) of a gray solid. ^{1}H NMR (DMSO-d_6 + TFA-d, 300 MHz) δ 9.43 (s, 2H), 9.14 (s, 2H), 7.94-7.85 (m, 4H), 4.84 (m, 1H), 3.84 (s, 4H), 3.55-3.42 (m, 6H), 2.16 (br m, 4H). MS (ESI) 360 (M+H).

Part E: <u>Methyl 2-(*n*-butyloxycarbonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionate hydrobromic acid salt.</u>

n-Butylchloroformate (45 μL, 0.35 mmol) was added to a solution of the intermediate of Part D (0.200 g, 0.33 mmol) and triethylamine (0.14 mL, 1.0 mmol) in dimethylformamide (2 mL) and the mixture was stirred at room temperature for 2 h. The solution was flash chromatographed using a gradient solvent system starting

with chloroform and progressing to 20 % methanol/chloroform in 5 % steps to give .249 g of the title compound. MS (ESI) 460 (M+H).

Part F: <u>2-(*n*-Butyloxycarbonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionic acid bis trifluoroacetic acid salt.</u>

The intermediate of Part E (229 mg, 0.33 mmol) was dissolved in methanol (7 mL) and water (7 mL) and lithium hydroxide hydrate (33 mg, 0.79 mmol). The mixture was stirred at room temperature for 24 h and additional lithium hydroxide hydrate (18 mg, 0.43 mmol) was added. The mixture was stirred for 24 h and the methanol was evaporated. The aqueous residue was diluted with trifluoroacetic acid (0.15 mL) and the mixture was purified by Prep HPLC as described in Example 514A, Part B to give 31 mg (11 %) of the title compound. ^1H NMR (DMSO-d_6, 300 MHz) δ 9.40 (br s, 2H), 9.12 (br s, 2H), 7.91-7.86 (m, 4H), 7.61 (br, 1H), 6.56 (br, 1H), 4.44 (br, 1H), 4.00 (t, J=6.2 Hz, 2H), 3.38 (m, 6H, under water peak), 2.03 (br, 4H), 1.58-1.54 (m, 2H), 1.36-1.34 (m, 2H), 0.90 (t, J=7.4 Hz, 3H). HRMS (FAB, glycerol) Calc. for $(M+H)^+$: 446.2403. Found: 446.2394.

Example 1541

2-(*R,S*)-(3-methylphenylsulfonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionic acid bis trifluoroacetic acid salt

Part A: <u>Methyl 2-(*R,S*)-(*m*-toluenesulfonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionate hydrobromic acid salt.</u>

m-Toluenesulfonyl chloride (63 mg, 0.33 mmol) was added to a mixture of the intermediate in Example SP1, Part D (0.200 g, 0.33 mmol) and triethylamine (0.14 mL, 1.0 mmol) in dimethylformamide (2 mL) and the mixture was

stirred at room temperature for 19 h. Additional *m*-toluenesulfonyl chloride (14 mg, 0,07 mmol) was added and the mixture was stirred for 24 h. The solution was flash chromatographed using a graduated solvent system starting with chloroform and progressing to 30 % methanol/chloroform to give 0.309 g of a tan solid. HRMS (FAB, glycerol) Calc. for $(M+H)^+$: 514.2124. Found: 514.2137.

Part B: <u>2-(*R,S*)-(*m*-Toluenesulfonylamino)-3-[3-(4-amidinophenyl)-1-oxo-2,8-diazaspiro[4.5]dec-2-en-8-yl]propionic acid bis trifluoroacetic acid salt.</u>

The intermediate of Part A (0.277 g, 0.46 mmol) was suspended in 6M hydrochloric acid and the mixture was stirred at room temperature for 2 d. The mixture was concentrated and the residue was purified by Prep HPLC as described in Example 514A, Part B to give 16 mg of the title compound. HRMS (FAB, glycerol) Calc. for $(M+H)^+$: 500.1968. Found: 500.1956.

Example 1552

5(*R,S*)-(2-Piperidin-4-yl)ethyl-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione

This material was prepared using the procedures outlined in Example 189, giving the title compound; mp: 133.4-135.1 °C; ^1H NMR (400 MHz, CD_3OD, 55 °C) δ 3.59 (t, J = 6.8 Hz, 2H), 3.50 (d, J = 17.7 Hz, 1H), 3.38 (bd, J = 12.9 Hz, 2H), 3.18 (d, J = 17.7 Hz, 1H), 2.98 (m, 4H), 2.85 (m, 2H), 2.50 (m, 1H, coincident with DMSO-d_5), 2.45 (m, 2H), 2.31 (t, J = 7.1 Hz, 2H), 2.00 (m, 2H), 1.98 (pentuplet, J = 7.1 Hz, 2H), 1.40 (m, 2H).

Example 1585A

N^2-n-butyloxycarbonyl-N^3-[3-(4-piperidinylmethyl)-isoxazolin-5-(R,S)-yl-acetyl]-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (DMSO) δ 8.5(1H, brd), 8.2(1H, brd), 8.0(1H, m), 7.4(1H, d), 4.7(1H, m), 3.9(3H, m), 3.6(1H, m), 3.25(2H, m), 3.1(3H, m), 2.9(2H, m), 2.7(1H, m), 2.4(2H, m), 2.2(3H, m), 1.8(2H, m), 1.7(1H, m), 1.5(2H, m), 1.3(4H, m), 0.9(3H, t)ppm; ESI mass spectrum 427.1 $(M+H)^+$ free base.sc577

Example 1603

Methyl N^2-n-butyloxycarbonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5(R,S)-yl-acetyl]-(S)-2,3-diaminopropionate TFA salt.

^{1}HNMR ($CDCl_3$) δ 6.29(1H, brd), 4.9(1H, m), 4.45(1H, m), 4.05(2H, m), 3.78(3H, s), 3.68(1H, m), 3.5(3H, m), 3.1(1H, m), 2.96(2H, m), 2.78(1H, m), 2.55(2H, m), 2.36(2H, m), 1.95(2H, m), 1.6(6H, m), 1.5(2H, m), 1.35(5H, m), 0.94(3H, m) ppm; ESI mass spectrum 455 $(M+H)^+$ free base.xw923

Example 1609

Methyl N^2-p-toluenesulfonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5-(R,S)-yl-acetyl]-(S)-2,3-diaminopropionate TFA salt.sc569

^{1}HNMR ($CDCl_3$) δ 7.7(2H, d), 7.3(2H, d), 7.18(1H, m), 6.4(1H, m), 4.92(1H, m), 4.0(2H,m), 3.7(1H, m), 3.58(3H, d), 3.35(2H, m), 3.1(1H, m), 2.9(2H, m), 2.75(1H, m), 2.55(1H, m), 2.4(6H, m), 1.9(2H, m), 1.6(5H, m), 1.35(2H, m)ppm; ESI mass spectrum 509.3 $(M+H)^+$ free base

Example 1619

N^2-(2-methylphenylsulfonyl)-N^3-[3-(4-piperidinylethyl)-isoxazolin-5-(R,S)-ylacetyl)-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (DMSO)δ: 8.5(1H, m), 8.18(1H, m), 8.05(1H, m), 7.79(1H, d J=8.057Hz), 7.51(1H, t, J=6.958 & 7.324Hz), 7.37(2H, m), 4.65(1H, m), 3.83(1H, m), 3.4(1H, m), 3.27(3H, m), 3.07(1H, m), 2.84(2H, m), 2.68(1H, m),

2.59(3H, s), 2.4(1H, m), 2.32(3H, m), 2.08(1H, m),1.83(2H, m), 1.45(3H, m), 1.26(2H, m)ppm; ESI mass spectrum 481.4 (M+H, 100)+ free base. se632

Example 1621

N^2-p-toluenesulfonyl-N^3-[3-(4-piperidinylethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.sc575

^{1}HNMR (DMSO) δ 7.73(2H, d), 7.35(2H, d), 4.85(2H, m), 4.05(1H, m), 3.63(1H, m), 3.2(2H, m), 3.0(4H, m), 2.6(1H, m), 2.4(3H, s), 2.42(2H, m), 2.0(2H, m), 1.7(1H, d), 1.6(3H, m), 1.4(3H, m)ppm; ESI mass spectrum 481 (M+H, 100)+ free base

Example 1622

N^2-(2-bromophenylsulfonyl)-N^3-[3-(4-piperidinylethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (DMSO)δ: 8.5(1H, brd), 8.2(1H, m), 8.1(1H, m), 7.95(1H, m), 7.8(1H, m), 7.5(2H, m), 4.7(1H, m), 3.9(1H, m), 3.4(1H, m), 3.25(2H, m), 3.2(1H, m), 3.0(1H, m), 2.8(2H, m), 2.7(1H, m), 2.4(2H, m), 2.3(2H, m), 2.2(1H, m), 1.8(2H, m), 1.5(2H, m), 1.2(2H, m)ppm; ESI mass spectrum 545.2 (M+H, 100)+ free base. se631

Example 1623

N^2-(3,5-dimethylisoxazoylsulfonyl)-N^3-[3-(4-piperidinylethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (DMSO)δ: 8.5(1H, d), 8.08(1H, m), 4.65(1H, m), 3.9(1H, m), 3.4(1H, m), 3.25(3H, m), 3.15(2H, m), 2.85(2H, m), 2.7(1H, m), 2.52(3H, s), 2.4(1H, m), 2.3(3H, m), 2.2(3H, m), 1.8(2H, brd, d), 1.45(3H, m), 1.25(2H, m)ppm; ESI mass spectrum 486.3 (M+H, 100)+ free base. se634

Example 1624

N^2-(3,4-dimethylthiazoylsulfonyl)-N^3-[3-(4-piperidinylethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (DMSO)δ: 8.6(1H, d), 8.45(1H, brd), 8.1(1H, m), 4.65(1H, m), 3.9(1H, m), 3.5(4H, m), 3.05(2H, m), 2.9(3H, m), 2.6(3H, s), 2.45(3H, s), 2.4(5H, m), 1.8(2H, brd. d), 1.5(2H, m), 1.2(2H, m)ppm; ESI mass spectrum 502.4 (M+H, 100)$^+$ free base. se104

Example 1625

N^2-n-butylsulfonyl-N^3-[3-(4-piperidinylethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.sc576

^{1}HNMR (DMSO) δ 8.5(1H, m), 8.2(2H, m), 7.55(1H, m), 4.7(1H, m), 3.9(1H, m), 3.4(1H, m), 3.2(3H, brd,d), 3.1(1H, m), 2.98(2H,m), 2.9(4H, m), 2.4(1H, d), 2.3(3H, m), 1.8(2H, brd, d),1.7(2H, m), 1.5(6H, m), 0.9(3H, t)ppm; ESI mass spectrum 447.3 (M+H, 100)$^+$ free base

Example 1627

N^2-n-butyloxycarbonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5-(R,S)-yl-acetyl]-(S)-2,3-diaminopropionic acid TFA salt

^{1}HNMR (DMSO) δ 8.5(1H, m), 8.2(2H, brd),7.3(1H, m),4.7(1H, m), 4.05(1H, m), 3.9(2H, t), 3.5(1H, m), 3.2(3H, brd,d), 3.0(1H, m), 2.8(2H, m), 2.7(1H, m), 2.4(1H, d), 2.25(3H, m),1.8(2H, d), 1.6(6H, m), 1.4(7H, m), 0.9(3H, t)ppm; ESI mass spectrum 441.3 (M+H, 100)$^+$ free base. sc574

Example 1631

N^2-p-toluenesulfonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.sc572

^{1}HNMR (CD_3OD)δ: 7.7(2H, m), 7.35(2H, m), 4.85(1H, m), 4.05(2H, m), 3.72(1H, m), 3.66(2H, m), 3.56(1H, m),

3.35(2H, m), 3.25(1H, m), 3.14(1H, m), 2.94(2H, m), 2.84(1H, m), 2.55(1H, m), 2.4(3H, m), 2.35(3H, m), 1.95(2H, m), 1.62(3H, m),1.32(4H, m),ppm; ESI mass spectrum 495.3 $(M+H)^+$ free base

Example 1656

N^2-m-toluenesulfonyl-N^3-[3-(4-amidinopiperidinyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminoproprionic acid se534

M.P. 70-74^{o}C; ^{1}H NMR (DMSO-d_6) δ 8.13 (m,2H), 7.58(m,2H), 7.44-7.38 (m, 5H), 4.74 (m,1H), 3.88-3.80 (m, 5H), 3.40 (m,1H), 3.14-2.99 (m,4H), 2.74 (m,2H), 2.37 (s,3H), 2.17 (dd, J=7.32,14.28 Hz), 1.88 (d,J=13.18 Hz, 2H), 1.53 (q, J=11.35 Hz, 2H) ppm; High Res Mass Spectrum calculated $(M+H)^+$ 495.202580;found $(M+H)^+$ 495.200904.

Example 1657

N^2-p-toluenesulfonyl-N^3-[3-(4-amidinopiperidinyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminoproprionic acid

Part A: The isoxazoline acetic acid was prepared starting from 1-t-butylcarbamate-4-piperidine carboxaldehyde (Jacobs, R.,et al, EP 532177) through methods previously described. ^{1}H NMR ($CDCl_3$) δ 4.94 (m, 1H), 4.18- 4.05 (m, 2H), 3.18 (dd, J=10.25,17.20 Hz, 1H), 2.90-2.67 (m, 4H), 2.63 (m, 2H), 1.87 (m, 2H), 1.56-1.45 (s, 9H), 1.46 (s, 9H) ppm; Mass Spectrum (NH_3-CI) m/z $(M+NH_4)^+$ 330 (100%); IR (KBr) 3100, 1734, 1690, 1648, 1430, 1276, 1168, 758 cm^{-1} .

Part B: The acid from Part A (360 mg, 1.2 mmol) was coupled with methyl L-N^2-p-toluylsulfonyl-diaminoproprionate using procedure described in Example 43D. The crude product was chromatographed on silica gel (2% MeOH/CH_2Cl_2) to afford 270 mg (41%) of a white foam. M.P. 55-60^{o}C; ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J=8.06 Hz, 2H), 7.30 (d, J=8.06 Hz, 2H), 6.45 (m, 1H), 5.73 (dd,

J=8.42,16.11 Hz, 1H), 4.90 (m, 1H), 4.13 (m, 2H), 4.01 (m, 1H), 3.58 (s, 3H), 3.60-3.49 (m, 2H), 3.10 (m, 1H), 2.84-2.72 (m, 3H), 2.57 (m, 2H), 2.48 (m, 1H), 2.42 (s, 3H), 1.85 (d, 2H), 1.55-1.46 (brd m, 2H), 1.46 (s, 9H)ppm; Mass Spectrum (NH_3-CI) m/z $(M+NH_4)^+$ 584 (100%); IR (KBr) brd 3300, 1746, 1688, 1428, 1238, 1164 cm^{-1}.

Part C: To the product from Part B (230 mg, 0.41 mmol) was added 10 ml of 30% TFA/CH_2Cl_2 and the mixture was stirred for 3h. The solvents were removed *in vacuo* . To the residue was added 2 ml DMF, triethylamine (0.39 ml, 2.8 mmol), and bis-tertbutyloxycarbonyl-3,5-dimethylpyrazole-1-carboxamidine (165 mg, 0.49 mmol) (Kim, et al, Tet. Lett., 1993, 34, 7677) and the mixture was stirred for 24h. The reaction was partitioned with EtOAc/water. The organic layer was washed successively with water, brine and dried ($MgSO_4$). Chromatography on silica gel (2% MeOH/CH_2Cl_2) afforded 203 mg (71%) of a white foam. M.P. 69-75°C; ^{1}H NMR ($CDCl_3$) δ 10.18 (brd m, 1H), 7.72 (d, J=8.05 Hz, 2H), 7.30 (d, J=8 Hz, 2H), 6.40 (m,1H), 5.65 (m, 1H), 4.87 (m, 1H), 4.30 (brd, 1H), 4.05 (brd, 1H), 3.60-3.51 (s+m, 5H), 3.09 (m, 3H), 2.78 (m, 3H), 2.42 (s, 3H), 1.89 (m, 2H), 1.73 (m, 2H), 1.63 (brd m, 2H), 1.49 (s, 18H)ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 709.5 (100%); IR (KBr) 3300-2800, 2210, 1742, 1660, 1600, 1546, 1446, 1332, 1162, 1092 cm^{-1} .

Part D: To the product from Part C (160 mg, 0.23 mmol) was added 6 ml of 1:1 MeOH/water and lithium hydroxide (28 mg, 0.67 mmol). The mixture was stirred for 18h and the solvents were removed *in vacuo*. The residue was taken up in water and acidified with 1N HCl and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered and concentrated to afford 118 mg (76%) of the acid. To the acid was added 10 ml 30% TFA/CH_2Cl_2 and the mixture was stirred 24h. The solvents were removed and the TFA salt was purified by HPLC to afford 20 mg product. M.P. 134-140°C; ^{1}HNMR (DMSO-d_6) δ 7.9 (q,1H),

7.66 (d,j=8.06 Hz, 2H), 7.46 (s, 3H), 7.36 (d,j=8.06 Hz, 2H), 4.72 (m,1H), 3.80 (d, j=13.18 Hz, 2H) 3.61 (m,1H), 3.41-3.18 (m, 5H), 3.13-2.99 (m,3H), 2.75 (m 2H), 2.36 (s,3H), 2.22 (m, 1H), 1.88 (d, j= 12.8Hz, 2H), 1.53 (m, 2H) ppm ; Mass spectrum (ESI) m/z 495.2 (100%), high res Mass Spectrum $(M+H)^+$ calculated 495.20258, found 495.202476

<u>Example 1673</u>

<u>N^2-p-toluenesulfonyl-N^3-[3-(4-amidinopiperidinylmethyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.</u>

^{1}HNMR (DMSO) δ: 8.1(2H, m), 7.65(2H, d), 7.35(2H, d), 4.7(1H, m), 3.8(3H, m), 3.4(2H, m), 3.1(1H, m), 3.0(3H, m), 2.7(1H, m), 2.4(1H, m), 2.35(3H, s), 2.25(1H, m), 2.2(3H, m), 1.85(1H, m), 1.7(2H, m), 1.6(1H, m), 1.2(3H, m)ppm; ESI mass spectrum 509.4 $(M+H, 100)^+$ free base. se103

<u>Example 1704</u>

<u>N^2-n-butyloxycarbonyl-N^3-[3-(guanidinopropyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionic acid TFA salt.</u>

Part A: The title compound was prepared following the [3+2] cycloaddition methodology employed for example 4 from the readily accessible Boc-aminopropylchlorooxime (obtained from a sequence of steps from commerical (Aldrich) aminopropanol (aldehyde obtained via Moffat et. al. J.C.S. Perk. Trans. 1. 1991, 5, 1041-1051)) and butylvinyl ester. LiOH saponification in methanol:water (9:1), then afforded the desired acetic acid compound in 90% yield. ^{1}HNMR ($CDCl_3$) δ: 4.90(m, 1H), 4.70(brd, s, 1H), 3.08(m, 3H), 2.68(m, 2H), 2.57(dd, 1H), 2.34(t,2H), 1.75(m, 2H), 1.41(s, 9H)ppm; ESI mass spectrum 287(M+H, 100).sd266

Part B: The product from part A was then coupled to methyl N^2-n-butyloxycarbonyl-(S)-2,3-diaminopropionate via

the procedure used in example 4, to obtain Methyl N^2-n-butyloxycarbonyl-N^3-[3-(Boc-aminopropyl)isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminopropionate in 50% yeild. Treatment with trifluoroaceticacid in dichloromethane, evaporation of solvent then afforded the anilino intermediate as the TFA salt. Standard guanidine formation techniques then afforded the di-Bocguanidinopropyl analog in 90% yield. Removal of the Boc-protecting groups with TFA afforded example 601 as the TFA salt. Alternatively, saponification of the methyl ester followed by removal of the Boc-protecting groups with TFA also afforded the desired product as the TFA salt in 80% overall yield. ^{1} H NMR (CD_3OD) δ: 4.93(m, 1H), 4.29(brd.m, 1H), 4.02(t, 2H), 3.65(m, 1H), 3.32(m, 1H), 3.21(m, 2H), 3.09(dd, J=10.2 &17.6Hz, 1H), 2.79(dd, J=7.32 &17.1Hz, 1H), 2.52(dd, J=2.2& 8.8Hz, 1H), 1.84(m, 2H), 2.39(m, 3H), 1.58(m, 2H), 1.36(m, 2H), 0.9(t,3H,)ppm; HR MS calcd. for ESI mass spectrum 529(M+H, 100) for free base. sc761

Example 1756

N^2-p-toluylsulfonyl-N^3-[3-(4-piperidinylmethylaminocarbonyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminoproprionic Acidse533

Part A: To a mixture of tert-butyl vinylacetic acid (11.2 g, 0.079 mol) and ethylchlorooximidoacetate (11.37 g, 0.075 mol,Aldrich) in a mixture of 2:1 THF/water at 0^0C was added sodium bicarbonate (19.9 g, 0.237 mol). The reaction was stirred for 3d at room temperature, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried with $MgSO_4$. The crude oil was chromatographed on silica gel (7:1 hexanes/ EtOAc) to afford 7.46 g (39%) of product as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.15 (m, 1H), 4.39 (q, J=7.32 Hz, 2H),3.43 (dd,J=10.99,17.58 Hz, 1H), 3.03 (dd, J=7.69,17.58 Hz, 1H),

2.81 (dd,J=5.86,16.11 Hz, 1H), 2.59 (dd,J=7.69,16.11 Hz, 1H),1.46 (s, 9H), 1.39 (t,J=7.32 Hz, 3H); Mass Spectrum (NH_3-CI) m/z $(M+H)^+$ 258 (12%), $(M+NH_4)^+$ 275 (100%).

Part B: The ethyl ester (3 g, 0.012 mol) from Part 1A was selectively hydrolyzed with LiOH (0.64 g, 0.015 mol) in 1.5:1 methanol/ water at 0^0C for 1.5h. The methanol was removed *in vacuo*. The aqueous residue was acidified with 10% citric acid and extracted with EtOAc and dried with $MgSO_4$. The crude solid was recrystallized with CH_2Cl_2/ hexanes to afford 2 g (75%) white crystals. mp 83-86^0C; ^{1}H NMR ($CDCl_3$) δ 5.23 (m, 1H), 3.44 (dd, J=10.98,17.58 Hz, 1H), 3.05 (dd, J= 8.05,17.95 Hz, 1H), 2.82 (dd, J=5.85,16.11 Hz, 1H), 2.64 (dd, J=7.32,16.11 Hz, 1H), 1,46 (s, 9H)ppm; Mass spectrum (NH_3-CI) m/z $(M+NH_4)^+$ 247 (90%).

Part C: 4-Aminomethyl piperidine (3.8 g, 0.034 mol, Aldrich) was selectively protected in 68% yield with carbobenzoxyimidazole using the method of Sharma, et al. (J. Med. Chem. 1989, 32, 357). To the crude 4-Cbz-aminomethyl piperidine (3 g, 0.012 mol) in 30 ml dioxane at 0^0C was added 13 ml of 1N sodium hydroxide and di-t-butyl dicarbonate (2.7 g, 0.013 mol). The reaction was stirred at room temperature for 48h. The dioxane was removed *in vacuo* and the residue was suspended in EtOAc and washed successively with 10% citric acid, sat'd $NaHCO_3$, brine and dried ($MgSO_4$). Recrystallization with CH_2Cl_2/ hexane afforded 1 g of white crystals (24%) mp 91-96^oC; ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 5H), 5.10(s, 2H), 4.60 (t, 1H), 4.20 (brd, 2H), 3.0 (brd, 2H), 2.75 (brd, 2H), 1.65 (d, 2H), 1.45 (s, 9H), 1.12 (brd, 2H)ppm; Mass spectrum (NH3-CI) m/z (M+H)+ 349 (31%), (M+H-56)+ 293 (100%); IR (KBr) 1698,1530 cm^{-1}; Analysis for C19H28N2O4 calc'd C:65.49, H:8.10, N:8.04; found C:65.78, H:7.82, N:8.06.

Part D: To the compound from part C (94 mg, 2.7 mmol) was added 50 ml EtOH and 100 mg of 10% Pd/C and the

mixture was hydrogenated at 40 PSI for 18h. Filtration and removal of the solvent afforded 569 mg (98%) solid. mp 84-88°C; ^{1}H NMR ($CDCl_3$) δ 4.70 (brd, 1H), 3.10 (d, 2H), 3.0 (t, 2H), 2.95 (brd, 2H), 2.64 (t, 2H), 1.70 (d, 2H), 1.46 (s, 9H), 1.20 (m, 2H) ppm; Mass spectrum (NH_3-CI) m/z $(M+H)^+$ 215 (100%); IR (KBr) 2972-2800, 1694 cm^{-1}.

Part E: To the acid from Part B (360 mg, 1.6 mmol) in 5 ml EtOAc was added triethylamine (0.67 ml, 4.80 mmol) followed by TBTU (560 mg, 1.73 mmol). After 15 minutes the amine from Part D (370 mg, 1.7 mmol) was added and the reaction was stirred for 24h. The reaction mixture was washed successively with 10% citric acid, water, sat'd $NaHCO_3$, brine and dried ($MgSO_4$). The residue was chromatogrphed on silica gel (3:2 Hexanes/EtOAc) to afford 0.41 g (61%) white foam. ^{1}H NMR ($CDCl_3$) δ 5.04 (m, 1H), 4.63 (d, J=13.18 Hz, 2H), 4.53 (d,J=13.18 Hz, 1H), 3.52-3.38 (m, 1H), 3.15-2.99 (m, 4H), 2.77 (m, 2H), 2.59-2.49 (m, 5H),1.78 (t, J=10.0 Hz 3H), 1.46 (s, 9H), 1.44 (s, 9H), 1.25 (m, 2H); Mass Spectrum (NH_3-CI) m/z (M+H)+ 426.3 (29%), (M+H-56)+ 370.2 (43%); IR (KBr) 2976, 2930, 1714, 1632, 1592, 1522, 1476,1452,1392, 1366, 1168cm^{-1}.

Part F: To the product of Part E (380 mg, 0.89 mmol) was added 10 ml of 30% TFA/CH_2Cl_2 and stirred for 4h. The solvents were removed and 10 ml dioxane was added. The mixture was cooled to 0°C and 2 ml of 1N NaOH was added followed by di-t-butyldicarbonate (0.22g, 0.98 mmol). The reaction was stirred for 48 h at room temperature. The reaction was concentrated and partitioned with EtOAc and water. The aqueous layer was acidified with 10% citric acid, extracted with EtOAc and dried ($MgSO_4$). The crude residue was chromatographed on silica gel (10% MeOH/CH_2Cl_2) to afford 0.23 g (69%) of a white foam. mp 159-165°C ^{1}H NMR (DMSO-d_6) δ 6.95 (t, J=5.86 Hz, 1H), 4.87 (m, 1H), 4.33 (d, J=13.18 Hz, 1H), 4.09 (d, J=13.90 Hz, 1H), 3.31 (m, 1H), 3.07 (t, J= 12.82 Hz, 1H), 2.99 (dd, J=3.66,8.05 Hz, 1H), 2.93 (dd, J= 3.66, 7.70 Hz, 1H), 2.82

(t, J= 5.86 Hz, 2H), 2.69 (t, 12.82 Hz, 1H), 2.39 (m, 1H), 2.27 (dd, J=7.69,14.6 Hz, 1H), 1.67-1.60 (m, 3H), 1.37 (s, 9H), 1.04 (t, J=13.5 Hz, 1H)ppm; Mass Spectrum (NH3-CI) m/z $(M+NH_4)^+$ 387 (100%); IR (KBr) 3352, 1692, 1630, 1588, 1518, 1448, 1210, 1176, 1140 cm^{-1} .

Part G: The product of Part F (217 mg, 0.59 mmol) was coupled with methyl L-N^2-p-toluylsulfonyl-diaminoproprionate according to procedure in Example 43D. The crude material was chromatographed on silica gel (2% $MeOH/CH_2Cl_2$) to afford 230 mg (63%) foam. ^1H NMR ($CDCl_3$) δ 7.72 (d, 2H), 7.30 (d, 2H), 6.40-6.32 (m, 1H), 5.1 (m, 1H), 4.70 (brd, 2H), 4.50 (d, 1H), 3.99 (brd, 1H), 3.65 (s, 3H), 3.50 (m, 2H), 3.15-2.99 (m, 3H), 2.85-2.55 (m 2H), 2.45 (s, 3H), 1.85 (brd, 4H), 1.46 (s, 9H), 1.29 (m, 2H)ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 624.5 (72%), $(M+H-56)^+$ 568.3 (98%).

Part H: The product of Part G (200 mg, 0.32 mmol) was hydrolyzed with lithium hydroxide (20 mg, 0.48 mmol) in 1:1 MeOH/water for 48h. The solvents were removed *in vacuo* and the residue dissolved in water, acidified with 10% citric acid, extracted with EtOAc and dried ($MgSO_4$). The crude acid was treated with 15 ml of 30% TFA/CH_2Cl_2 for 24h. The crude TFA salt was purified via HPLC to give 21 mg (11%) foamy solid. ^1HNMR (DMSO-d_6) δ 8.15 (m,1H), 7.73 (m,1H), 7.63 (d,j=8.06 Hz, 2H), 7.35 (d,j=8.05 Hz, 2H), 4.90 (m,1H), 4.37 (d,j=13.5 Hz, 2H), 4.14 (d,j=2H, j=10.9 Hz), 3.83 (q,j=9 Hz,1H), 3.35 (m,2H), 3.12-2.90 (m,3H), 2.74 (m, 2H), 2.33 (s,3H), 2.50-2.20 (m, 3H), 1.90-1.70 (m,4H), 1.35(m,2H) ppm; High Res Mass Spectrum $(M+H)^+$ calculated 510.202246, found 510.203464.

Example 1769

N^2-p-toluenesulfonyl-N^3-[3-(N-(4-piperidinylmethyl)-N-(methyl)aminocarbonyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminoproprionic Acid Trifluoroacetic Acid Saltse536

Part A: To 4-tertButyloxycarbonyl-piperidinyl-methyl amine described previously (1.93 g, 0.009 mol) in 20 ml CH_2Cl_2 at 0^oC was added pyridine (1.1 ml, 0.014 mol) followed by slow addition of trifluoroacetic anhydride (1.4 ml, 0.009 mol). The reaction was stirred at 0^oC for 1h, then it was diluted with CH_2Cl_2 washed successively with 10% citric acid, water, sat'd $NaHCO_3$, brine and dried ($MgSO_4$). Recrystallization from CH_2Cl_2/Hexanes afforded 2.4 g (86%) of a bright yellow solid. mp 123-125 ^oC; ^1H NMR ($CDCl_3$) δ 4.74 (m, 1H), 4.56 (d, J=13 Hz, 1H), 4.0 (d, J= 12 Hz, 1H), 3.14 (m, 3H), 2.75 (t, J=13 Hz,1H), 1.82 (d, 3H), 1.45 (s, 9H) 1.28 (m, 2H) ppm; Mass Spectrum (NH_3-CI) m/z $(M+NH_4)^+$ 328 (100%),$(M+NH_4$ $-56)^+$ 272.1 (100%); IR (KBr) 3354, 1686, 1526, 1200, 1140 cm^{-1} .

Part B: To the product of Part A (400 mg, 1.29 mmol) in 2 ml DMF was added NaH (62mg, 1.6 mmol) After 1h, methyl iodide (0.1 ml, 1.6 mmol) was added and the reaction was immersed in a 60^0C oil bath for 24h. The reaction was cooled and partioned between EtOAc and water. The organic layer was washed with water, brine and dried ($MgSO_4$). The reaction had not gone to completion and was resubjected to the above conditions and after work up afforded 322mg (77%) yellow oil. The crude trifluoroacetate was placed in 20 ml of 1:1 MeOH/ water and K_2CO_3 (150 mg, 1.1 mmol) was added and the reaction was stirred for 36h. The solvents were removed *in vacuo* and the residue partioned with EtOAc/water. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine and dried ($MgSO_4$), filtered and concentrated to yield 194 mg (89%) oil. ^1H NMR (CDCl3) δ 3.15 (m, 4H), 2.85 (s, 3H), 2.80 (brd s, 1H), 2.61 (t, J= 12Hz, 2H), 1.63 (d, J= 10.6 Hz, 2H), 1.45 (s, 9H), 1.25 (m, 2H), 0.87 (m, 1H)ppm; Mass Spectrum (NH_3-CI) m/z $(M+H)^+$ 229 (100%), $(M+NH_4)^+$ 246 (15%); IR (KBr) 2924,1696,1160 cm^{-1} .

Part C: The product of Part B (173 mg, 0.76 mmol) was coupled with the acid (from Part B previous example) according to procedure in Example 43D to yield 177 mg (54%) yellow oil. ^1H NMR ($CDCl_3$) δ 5.02 (m, 1H), 4.59-4.50 (brd m, 2H), 3.48 (dd, J= 10.62,17.58 Hz, 1H), 3.15-3.02 (m, 4H), 2.86 (s, 3H), 2.77 (m, 2H), 2.59 (m, 1H), 2.0-1.91 (brd m, 1H), 1.73 (t, J=11.72 Hz, 2H), 1.46 (s, 18H), 1.28 (m, 2H) ppm; Mass Spectrum (NH_3-CI) m/z $(M+H)^+$ 440.2 (100%), $(M+NH_4)^+$ 457.3 (23%), $(M+H-56)^+$ 384.2 (73%); IR (KBr) 2976, 2932, 1730, 1694, 1634, 1162 cm^{-1}

Part D: The product of Part C (170 mg, 0.387 mmol) was deprotected and selectively reprotected as in Part 1F to afford a yellow foam. ^1H NMR ($CDCl_3$) δ 5.10 (m, 1H), 4.60 (m, 1H), 4.50 (m, 1H), 3.50 (m, 1H), 3.12 (m, 4H), 2.80 (s, 3H), 2.78 (m, 1H), 2.70 (m, 2H), 1.90 (brd m, 1H), 1.75 (brd m, 2 H), 1.45 (s, 9H), 1.25 (brd m, 2H)ppm; Mass Spectrum (NH_3-CI) m/z $(M+NH_4)^+$ 401 (100%).

Part E: The product of Part D (148mg, 0.386 mmol)was coupled with methyl L-N^2-p-toluylsulfonyl-diaminoproprionate according to the procedure in Example 43D. The crude material was chromatographed on silica gel (3% MeOH/CH_2Cl_2) to afford 230 mg clear glass containing minor impurities. ^1H NMR ($CDCl_3$) δ 7.72 (d,2H), 7.33 (d,2H), 6.35 (m, 1H), 5.10 (m,1H), 4.61 (brd m, 1H), 4.45 (brd m, 1H), 3.97 (brd m, 1H), 3.63-3.54 (s+m, 5H), 3.48-3.30 (m, 2H), 3.15 (brd m,4H), 2.85 (s, 3H), 2.75-2.5 (m, 4H), 2.45 (s, 3H), 1.78 (brd m, 2H), 1.46 (s,9H), 1.30 (m, 2H) ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 638.5 (100%)

Part F: The product of Part E (230 mg, 0.36 mmol) was subjected to hydrolysis and deprotection and purification by HPLC to afford 134 mg (58%) of a white powder. mp 69-72^oC; ^1HNMR (DMSO-d_6) δ 8.35 (brd m, 2H), 8.10 (brd m, 2H), 7.65 (d, J=6.96 Hz, 2H), 7.35 (d, j=8.05 Hz, 2H), 4.83 (m,1H), 4.36 (d,j=13.6 Hz, 1H), 4.12 (d,j=10 Hz, 1H), 4.0-3.5 (m,6H), 3.35 (m,1H), 3.14 (t,j=10.98 Hz, 1H),2.83 (m,1H), 2.59 (s, 3H), 2.55 (m,1H), 2.36 (s, 3H), 2.35

(m,1H), 2.0 (brd m,1H), 1.80-1.74 (brd m, 2H), 1.18 (m, 2H) ppm; Mass Specturm (ESI) m/z $(m+H)^+$ 524.4 (100%); IR (KBr) 3300-2800 brd, 1736,1632, 1202,1162 cm^{-1}.

Example 1774

N^2-p-toluylsulfonyl-N^3-[3-(4-piperidinylaminocarbonyl)-isoxazolin-5-(R,S)-ylacetyl]-(S)-2,3-diaminoproprionatese535

Part A: The acid (from Part B described previously, 225mg, 0.98 mmol) was coupled with 1-tertbutyloxycarbonyl-4-aminopiperidine (Obase, H; et al, J.Het. Chem. 1983, 20, 565) as described in Example 43D.A white foam was obtained in 78% yield. ^1H NMR ($CDCl_3$) δ 6.50 (d, J=8.05 Hz, 1H), 5.13 (m, 1H), 3.43 (dd, J= 10.62, 17.95 Hz, 1H), 3.04 (dd, J=7.69, 18.3 Hz, 1H), 2.87 (t, J=12.45 Hz, 2H), 2.76 (dd, J= 6.22, 16.11 Hz, 1H), 2.57 (dd, J=6.95, 16.11 Hz, 1H), 1.94 (d, J=9.88 Hz, 2H), 1.46 (s,18H), 1.41 (m, 2H)ppm; Mass Spectrum (NH_3-CI) m/z $(M+H)^+$ 412.2 (69%), $(M+NH_4)^+$ 429.3 (50%), $(M+NH_4-56)^+$ 373.2 (100%); IR (KBr) 3424,2866,1728,1692,1536,1426,1368,1238,1162 cm^{-1} .

Part B: The product of Part A (300 mg, 0.73 mmol) was deprotected with TFA and selectively reprotected with di-t-butyldicarbonate to afford 270 mg of a white foam. ^1H NMR ($CDCl_3$) δ 6.64 (d, J=8.05 Hz, 1H), 5.2 (m, 1H), 4.10-3.95 (m, 3H), 3.47 (dd, J=10.99, 17.96 Hz, 1H), 3.08 (dd, J=7.69, 17.95 Hz, 1H), 2.89 (t+dd, 3H), 2.72 (dd, J= 6.95, 16.11 Hz, 1H), 1.94 (d, J=12.82 Hz, 2H), 1.46 (s, 9H), 1.46 (brd m, 2H)ppm; Mass Spectrum (NH_3-CI) m/z $(M+NH_4)^+$ 373 (100%).

Part C: The product of Part B (260 mg, 0.73 mmol) was coupled with methyl L-N^2-p-toluylsulfonyl-diaminoproprionate according to the procedure in Example 43D. The crude foam was chromatographed on silica gel (2% MeOH/CH_2Cl_2) to afford 289 mg (65%) of a white foam. ^1H NMR ($CDCl_3$) δ 7.71 (d, J=8.06 Hz, 2H), 7.31 (d, J=8.42 Hz, 2H), 6.65 (dd, J=6.59 Hz, 1H), 6.36 (t, J=5.86 Hz, 1H),

5.15 (m, 1H), 4.10-3.96 (m, 4H), 3.63-3.56 (s+m, 5H), 3.45-3.35 (m, 1H), 3.09 (m,1H), 2.85 (t, J=12.45 Hz, 2H), 2.62 (m, 2H), 2.43 (s, 3H), 1.94 (d, J=12.82 Hz, 2H), 1.45 (s+m, 9+2H)ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 610.3 (100%).

Part D: The product of Part C (289 mg, 0.47 mmol) was subjected to hydrolysis and deprotection and purification as previously described to afford 224 mg (78%) white powder. mp 88-91°C; ^{1}HNMR (DMSO-d_6) δ 8.66-8.57 (d+m, j=7.69Hz, 2H), 8.30 (brd m, 1H), 8.07 (m, 2H), 7.64 (d,j=8.06 Hz, 2H), 7.35 (d,j=8.06 Hz, 2H), 4.94 (m,1H), 3.96 (m, 1H), 3.87 (q,j=6.95 Hz, 1H), 3.30-3.24 (m,4H), 3.08-2.89 (m,4H), 2.46 (m,1H), 2.37 (s,3H), 2.37 (m,1H), 1.87 (d,j=10.9 Hz,2H), 1.73 (q,j=10.6 Hz,2H) ppm; Mass Spectrum (ESI) m/z $(M+H)^+$ 496.3 (100%); IR (KBr) 3300-2800 brd, 1736,1666, 1544 1162 cm^{-1}

Example 1945

<u>N^2-3-Methylphenylsulfonyl-N^3-[3-[2-(piperidin-4-yl)ethyl]isoxazolin-5(*R,S*)-ylacetyl)-(*S*)-2,3-diaminopropionic Acid TFA Salt</u>

Part A: <u>Methyl (3-(2-*N*-*t*-Butyloxycarbonylpiperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetate</u>

To a solution of Methyl Vinylacetate 352 g, 0.35 mol) in CH_2Cl_2 (175 mL) was added a 5% solution of sodium hypochlorite (210 mL, 0.15 mol). The mixture was stirred rapidly at room temperature and a solution of (3-*N*-*t*-butyloxycarbonylpiperidin-4-yl)propanal oxime (Example 189, Part B, 17.60 g, 68.6 mmol) in CH_2Cl_2 (50 mL) was added over 15 h. The mixture was diluted with water and CH_2Cl_2, the layers separated, and the aqueous washed with CH_2Cl_2. The combined organic was dried ($MgSO_4$), concentrated *in vacuo*, and the oily residue purified using flash chromatography (10-50% EtOAc/hexanes step gradient), giving 10.35 g (42%) of the desired isoxazoline as a

golden oil; Anal. Calcd for $C_{18}H_{30}N_2O_5$: C, 61.00; H, 8.53; N, 7.90. Found: C, 61.07; H, 8.50; N, 7.80.

Part B: <u>(3-(2-*N*-*t*-Butyloxycarbonylpiperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetic Acid</u>

To a solution of methyl (3-(2-*N*-*t*-butyloxycarbonylpiperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetate (10.35 g, 29.20 mmol) in THF (100 mL) was added 0.5 M LiOH (80 mL, 40 mmol). The resulting solution was stirred at room temperature overnight (18 h) and then concentrated *in vacuo* to one-half volume. The pH was adjusted to 4, and the resulting cloudy solution washed with CH_2Cl_2 (4 x 30 mL). The combined organic was dried ($MgSO_4$), concentrated *in vacuo*, and placed under vacuum until constant weight was achieved, affording 9.74 g (98%) of the desired acid; Anal. Calcd for $C_{17}H_{28}N_2O_5$: C, 59.98; H, 8.29; N, 8.23. Found: C, 60.19; H, 8.42; N, 7.87.

Part C: <u>*t*-Butyl N^2-3-Methylphenylsulfonyl-N^3-[(3-(*N*-*t*-butyloxycarbonyl-2-piperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate</u>

To a solution of (3-(2-*N*-*t*-butyloxycarbonylpiperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetic acid (165 mg, 0.485 mmol) and *t*-butyl N^2-3-methylphenylsulfonyl-(*S*)-2,3-diaminopropionate hydrochloride (170 mg, 0.485 mmol) in DMF (5 mL) was added Et_3N (0.2 mL, 1.4 mmol) followed by TBTU (160 mg, 0.498 mmol). The resulting mixture was stirred for 4 h at room temperature, then was diluted with EtOAc (50 mL). It was washed with water (4 x 20 mL), sat. $NaHCO_3$ (30 mL), sat. NaCl and dried ($MgSO_4$). Concentration *in vacuo* followed by placing the material under vacuum until constant weight was achieved afforded 271 mg (88%) of the desired amide; MS (ESI, e/z, relative intensity): 637 $(M + H)^+$, 20%, 537 $(M + H - C_4H_9CO_2)^+$, 51%.

Part D: N^2-3-Methylphenylsulfonyl-N^3-[(3-(2-piperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid TFA Salt

To a solution of *t*-butyl N^2-3-methylphenylsulfonyl-N^3-[(3-(*N*-*t*-butyloxycarbonyl-2-piperidin-4-yl)ethyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate (261 mg, 0.410 mmol) in CH_2Cl_2 (2 mL) was added TFA (2 mL, 26 mmol). After 2 h at room temperature, the solution was concentrated *in vacuo* and the residue triturated with ether (3 x 5 mL). The resulting white powder was purified using reverse phase HPLC, giving 202 mg (83%) of the desired piperidine; MS (ESI, e/z, relative intensity): 481 $(M + H)^+$, 100%.

Example 2103

N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate Trifluoroacetate Salt

Part A: Methyl N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3[3-(4-*N*-*t*-butoxycarbonylamidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate

Methyl N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3-Boc-(*S*)-2,3-diaminopropionate (1.40 mmole) was stirred with 4 *M* HCl/dioxane (10 mL, 40 mmol) at 25°C. After 2.5 h, the volatiles were removed *in vacuo*, and residual HCl/dioxane was removed by repeated addition of toluene and evaporation. To the residue was added 3-(4-*N*-*t*-butoxycarbonylamidinophenyl)isoxazolin-5(*R,S*)-ylacetic acid (510 mg, 1.47 mmol), TBTU (480 mg, 1.50 mmole) and DMF (15mL). Triethylamine (0.830 mL, 603 mg, 5.97 mmole) was added and the reaction mixture was stirred at 25°C overnight. The mixture was diluted with water (70 mL) extracted with 3 X ethyl acetate. The combined organic extracts were washed with 2 X water, 5% pH 4 potassium hydrogen phthalate buffer (25 mL), 5% aqueous sodium

bicarbonate (25 mL) and brine. After drying over MgSO4, removal of volatiles and purification by flash chromatography (ethyl acetate) provided 0.598 g of the desired product in 96% purity, as assessed by analytical HPLC (4.6 mm X 25 cm C18 reverse phase, 1 mL/min, 0.05% TFA/10-90% AcCN/water gradient over 20 min, product at 12.9 min); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.63 (m, 2H), 6.52 (bm, 1H), 6.07 (bd, 1H), 5.11 (bm, 1H), 4.02 (bm, 1H), 3.66/3.67 (2s, 3H, diastereomers, methyl ester), 3.67-3.45 (m, 3H), 3.15 (m, 1H), 2.60/2.61 (2s, 3H, diastereomers, isoxazole methyl), 2.76-2.55 (m, 2H), 2.38/2.41 (2s, 3H, diastereomers, isoxazole methyl), 1.56 (s, 9H, *t*-Bu); MS (ESI): *m/e* 607.2 $(M+H)^+$.

Part B: N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3[3-(4-*N*-*t*-butoxycarbonylamidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate

To a solution of 200 mg (0.329 mmole) of methyl N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3[3-(4-*N*-*t*-butoxycarbonyl-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diamino-propionate in 15 mL of THF/MeOH/water 1:1:1 was added 138 mg (3.29 mmole) of LiOH. After 2 h, analytical HPLC (see conditions in Part A, product at 11.7 min) indicated the reaction was 97% complete. Removal of volatiles and purification by flash chromatography provided 0.164 g 91% pure (see HPLC conditions in Part A) of the desired product as a mixture of free acid and lithium salt (as indicated by 0.55% Li by elemental analysis); ^1H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 8.0 Hz, 2H), 7.96 (m, 1H), 7.75 (dd, J = 1.5, 8.4 Hz, 2H), 5.02 (m, 1H), 3.58-3.08 (m, 5H), 2.55 (s, 3H, isoxazole methyl), 2.60-2.37 (m, 2H), 2.34 (s, 3H, isoxazole methyl), 1.45 (s, 9H, *t*-Bu); MS (ESI): *m/e* 593.3 $(M+H)^+$, *m/e* 493.2 $(M-Boc)^+$.

Part C: N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diaminopropionate Trifluoroacetate Salt

A solution of 137 mg (0.231 mmole) of N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3[3-(4-*N*-*t*-butoxycarbonyl-amidinophenyl)isoxazolin-5(*R,S*)-ylacetyl]-(*S*)-2,3-diamino-propionate in 4 mL of CH_2Cl_2 and 2 mL of TFA was stirred for 4 h, then diluted with 60 mL of ether. The precipitate was dried to give 0.103 g of the desired product as a white solid, which was determined to be 96% pure by analytical HPLC (see HPLC conditions in Part A); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (bs, 1H), 9.72 (bs, 1H), 9.29 (bs, 2H), 8.25 (bs, 1H), 8.16 (m, 1H), 7.87 (s, 4H), 5.02 (bm, 1H), 3.78 (bs, 1H), 3.60-3.08 (m, 4H), 2.54 (s, 3H, isoxazole methyl), 2.34 (s, 3H, isoxazole methyl), 2.62-2.34 (m, 2H); MS (ESI): *m/e* 493.3 $(M+H)^+$; HRMS (FAB): *m/e* calculated for $C_{20}H_{25}N_6O_7S$ $(M+H)^+$ 493.150544; found 493.148681.

Example 2103a

N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionate Trifluoroacetate Salt (Alternative Hydrolysis Procedure)

Methyl N^2-(3,5-dimethylisoxazole-4-sulfonyl)-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionate hydrochloride salt (Part B, replacing ammonium acetate with ammonium chloride, 1.3 g, 2.6 mmol) was stirred in 6N HCl (150 ml) at room temperature for 20 hours. Solvent was evaporated under reduced pressure to give the crude hydrochloride salt as a white solid (1.1 g, 87%). Purification of 0.17 g crude product by preparative HPLC (Vydac C18 reverse phase column; 2 x 25 cm; 10 ml/min flow rate; 254 nM; gradient: from 100% H_2O with 0.05% TFA to 20% H_2O and 80% CH_3CN with 0.05% TFA in 50 minutes) yielded 0.12 g (70.6%) of the title compound as a white

powder. Chiral HPLC analysis (SFC, Chiralcel OD; 0.46 x 25 cm; 30^{o}C; 2.0 ml/min flow rate; 0.1% TFA/22% MeOH/78% CO_2; 280 nM; 150 atm) showed >99% d.e. with respect to the (*S,S*)-diastereomer and >98% chemical purity. MS (ESI): *m/e* 493 $(M+H)^+$. HRMS (FAB): *m/e* calculated for $C_{20}H_{24}N_6O_7S$ $(M+H)^+$ 493.150649; Found 493.150544.

Example 2103b

N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3-[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid Methanesulfonate Salt

Part A: Methyl N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3[3-(4-(cyanophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionate

To a suspension of 3-(4-cyanophenyl)isoxazolin-5(*R*)-ylacetic acid (252 mg, 0.725 mmol), methyl N^2-(3,5-dimethylisoxazole-4-sulfonyl-(*S*)-2,3-diaminopropionate hydrochloride (28.24 g, 70% purity, 63.0 mmol) in DMF (200 mL) was added TBTU (28.90 g, 90 mmol). The mixture was cooled to 0 °C and Et_3N (31.4 mL, 225 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature overnight (18 h), then was diluted with EtOAc (500 mL). It was washed with water (4 x 200 mL), sat. $NaHCO_3$ (100 mL), sat. NaCl (100 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by placing the material under vacuum until constant weight was achieved afforded 25.06 g (81%) of the desired amide; ^1H NMR (300 MHz, $CDCl_3$) δ 8.77 (bs, 1H), 8.22 (t, J = 5.9 Hz, 1H), 5.02 (m, 1H), 3.98 (t, J = 7.0 Hz, 1H), 3.55 (dd, J = 17.2, 10.6 Hz, 1H), 3.48 (s, 3H), 3.42 (m, 1H), 3.16 (m, 2H), 2.54 (s, 3H, coincident with m, 1H, DMSO-d_5), 2.37 (dd, J = 14.6, 7.0 Hz, 1H), 2.33 (s, 3H).

Part B: Methyl N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionate Acetate Salt

Into a solution of methyl N^2-(3,5-dimethyl-isoxazole-4-sulfonyl)-N^3[3-(4-(cyanophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionate (25.06 g, 51.17 mmol) in anhydrous MeOH (750 mL) at 0 °C was bubbled HCl gas for 3 hours. The resulting solution was then allowed to warm to room temperature overnight (18 h), after which the solvent was evaporated *in vacuo*, to give an oil. The oily residue was triturated with ether (3 x 100 mL) and the resulting solid placed under vacuum until constant weight was achieved. The crude imidate was then dissolved in MeOH (1 L) and ammonium acetate (20.0 g, 259 mmol) added. The resulting mixture was stirred at room temperature for 18 h, then concentrated *in vacuo*. The residue was then crystallized from EtOH, giving 21.75 g of crude amidine. A portion of this material (8.5 g) was purified using flash chromatography (20% MeOH-EtOAc) to give 3.77 g (33%) of 97.6% pure amidine (analytical HPLC: 4.6 mm X 25 cm C18 reverse phase, 1 mL/min, 0.05% TFA/10-90% AcCN/water gradient over 20 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (bt, 1H), 7.86 (m, 4H), 5.01 (m, 1H), 3.96 (t, J = 6.6 Hz, 1H), 3.56 (dd, J = 17.2, 10.6 Hz, 1H), 3.48 (s, 3H, coincident with m, 1H), 3.18 (m, 2H), 2.53 (s, 3H, coincident with m, 1H, DMSO-d_5), 2.54 (s, 3H), 2.36 (dd, J = 14.6, 7.0 Hz, 1H), 2.32 (s, 3H), 1.74 (s, 3H); MS (ESI): *m/e* 507.3 $(M+H)^+$.

Part C: N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid (Enzymatic Hydrolysis)

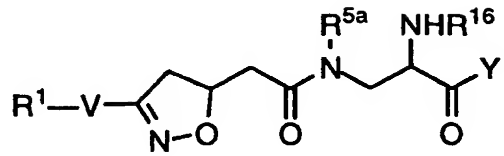
To a solution of methyl N^2-(3,5-dimethylisoxazole-4-sulfonyl-N^3[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionate HOAc salt (1.866 g, 3.29 mmol) in 0.4 *N* Hepes buffer (pH 7.1, 220 mL, 15 mmol) was added

rabbit liver esterase (3.6 *M* crystalline suspension in ammonium sulfate, 2000 units, Sigma). The resulting solution was incubated at 37 °C for 60 hours. Protein was removed from the reaction mixture by ultra filtration (Amicon YM-10 membrane), and the filtrate was then concentrated *in vacuo* and lyophilized. Purification using a reverse phase silica column (5 x 9.5 cm in water; crude product loaded as an aqueous solution followed by elution with water (1200 mL) and by 500 mL each of 5, 10, 20 and 30% CH_3CN-H_2O. Fractions containing the desired product were pooled, acetonitrile was removed and the aqueous solution lyophilized to yield 1.5 g (93 %) of pure zwitterion; ^1H NMR (300 MHz, DMSO-d_6) δ 7.93 (t, 1H), 7.76 (s, 4H), 4.98 (m, 1H), 3.17-3.50 (m, 5H, coincident with water), 2.66 (dd, 1H), 2.56 (s, 3H), 2.35 (s, 3H), 2.36 (dd, 1H); MS (ESI): *m/e* 493.3 $(M+H)^+$.

Part D: <u>N^2-(3,5-Dimethylisoxazole-4-sulfonyl)-N^3[3-(4-amidinophenyl)isoxazolin-5(*R*)-ylacetyl]-(*S*)-2,3-diaminopropionic Acid Methanesulfonic Acid Salt</u>

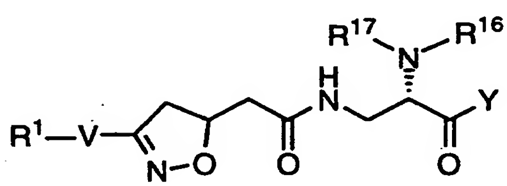
To a solution of the zwitterion (2.75 g, 5.43 mmol) in 50% CH_3CN-H_2O (135 mL) was added methanesulfonic acid (0.57 g, 5.97 mmol). The reaction mixture was stirred at room temperature for 1 h, resulting in a clear solution. Solvents were removed *in vacuo* and the residue placed under vacuum for several hours. The crude mesylate was dissolved in hot acetone and water until the solution was clear (120 mL total volume). After hot filtration the solution was allowed to cool slowly and was then refrigerated for 24 h. The resulting white precipitate was filtered and dried under vacuum, affording 1.72 g (52%) of the title compound; ^1H NMR (300 MHz, DMSO-d_6) δ 9.37 (bs, 2H), 9.03 (bs, 2H), 8.57 (d, J = 9.5 Hz, 1H), 8.23 (t, J = 5.9 Hz, 1H), 7.88 (s, 4H), 5.03 (m, 1H), 3.91 (m, 2H), 3.57 (dd, J = 17.2, 10.6 Hz, 1H), 3.44 (m, 1H), 3.21 (dd, J = 17.6, 7.7 Hz, 1H), 3.09 (m, 1H), 2.58 (dd, J

Table 2B



Example Number	R^1–V	R^{5a}	R^{16}	Y	MS $(M+H)^+$
651	4-amidinophenyl	methyl	benzyloxycarbony	OMe	496
652	4-amidinophenyl	methyl	n-butyloxycarbony	OMe	
653	4-amidinophenyl	methyl	3-methylphenylsulfonyl	OMe	
654	4-amidinophenyl	methyl	benzyloxycarbonyl	OH	
655	4-amidinophenyl	methyl	n-butyloxycarbonyl	OH	
656	4-amidinophenyl	methyl	3-methylphenylsulfonyl	OH	
657	4-amidinophenyl	methyl	4-methylphenylsulfonyl	OH	
658	4-amidinophenyl	methyl	4-methylphenylsulfonyl	OMe	
659	4-amidinophenyl	methyl	n-butylsulfonyl	OH	
660	4-amidinophenyl	methyl	n-butylsulfonyl	OMe	

Table 2C



Example Number	R^1–V	R^{16}	R^{17}	Y	MS $(M+H)^+$
661	4-amidinophenyl	benzyloxycarbonyl	methyl	OMe	
662	4-amidinophenyl	benzyloxycarbonyl	methyl	OH	
663	4-amidinophenyl	n-butyloxycarbonyl	methyl	OMe	
664	4-amidinophenyl	n-butyloxycarbonyl	methyl	OH	
665	4-amidinophenyl	3-methylphenylsulfonyl	methyl	OMe	
666	4-amidinophenyl	3-methylphenylsulfonyl	methyl	OH	502
667	4-amidinophenyl	4-methylphenylsulfonyl	methyl	OMe	

Example 2423

N^2-n-butyloxycarbonyl-N^3-[3-(4-piperidinylpropyl)-isoxazolin-5-(R,S)-ylformyl]-(S)-2,3-diaminopropionic acid TFA salt.

^{1}HNMR (CD3OD)δ: 4.92(1H, m), 4.3(1H, m), 4.05(2H, m), 3.6(2H, m), 3.38(3H, m), 3.15(1H, m), 2.95(2H, m), 2.35(2H, m), 1.95(2H, m), 1.6(5H, m), 1.35(6H, m), 0.95(3H, m) ppm; ESI mass spectrum 427.3 $(M+H)^+$ free base.sc573

Example 2500

Methyl N^3-Boc-(*S*)-2,3-diaminopropionate

Part A: Methyl N^2-Cbz-*L*-2,3-diaminopropionate HCl Salt

To a solution of N^2-Cbz-*L*-2,3-diaminopropionic acid (Bachem, 220 g, 0.923 mol) in MeOH (2 L) at 0 °C was added thionyl chloride (76 mL, 1.04 mol) over 20 min. The solution was warmed to room temperature overnight (18 h) and then concentrated to give a solid. The solid was crystallized from $CHCl_3$-MeOH to give 172 g (64%) of the desired ester; ^{1}H NMR (DMSO-d_6) δ 8.38 (b, 3H), 7.96 (d, 1H), 7.38 (m, 5H), 5.05 (s, 2H), 4.44 (m, 1H), 3.66 (s, 3H), 3.14 (m, 2H).

Part B: Methyl N^2-Cbz-N^3-Boc-*L*-2,3-diaminopropionate

To a solution of methyl N^2-Cbz-(S)-2,3-diaminopropionate HCl salt (172 g, 0.596 mol) and di-*tert*-butyl dicarbonate (129.05 g, 0.591 mol) in CH_2Cl_2 (2 L) cooled in an ice bath was added a saturated solution of $NaHCO_3$ (1200 mL, 0.96 mol) and the solution was warmed to room temperature overnight (18 h). The layers were separated and the aqueous washed with CH_2Cl_2 (2 x 500 mL). The combined organic was washed with brine, dried ($MgSO_4$), and concentrated. The resulting white solid was triturated with hexanes (3 x 500 mL) and dried under vacuum, giving 195.99 g (93%) of the desired material; ^{1}H NMR (DMSO-d_6):

δ 7.60 (d, 1H), 7.35 (m, 5H), 6.88 (t, 1H), 5.02 (s, 2H), 4.14 (m, 1H), 3.60 (s, 3H), 3.28 (m, 2H), 1.37 (s, 9H).

Part C: Methyl N^3-Boc-(*S*)-2,3-diaminopropionate

To a solution of methyl N^2-Cbz-N^3-Boc-(S)-2,3-diaminopropionate. (54.7 g, 0.155 mol) in EtOH (300 mL) was added 10% Pd/C (4.0 g). The mixture was placed on a Parr apparatus and hydrogenated at 50 p.s.i. overnight (18 h). The catalyst was filtered through Celite®, the filter cake washed with EtOH (3 x 50 mL) and the filtrate was concentrated *in vacuo* and placed under vacuum to give 32.63 g (96%) of the free base amine as a golden, viscous liquid; ^{1}H NMR (DMSO-d_6): δ 8.20 (s, 1H), 6.90 (t, 1H), 5.36 (b, 3H), 3.61 9s, 3H), 3.51 (t, 1H), 3.18 (t, 2H), 1.38 (s, 9H).

Example 2502

Resolution of 3-(4-cyanophenyl)isoxazolin-5(R,S)-ylacetic acid by Crystallization

3-(4-Cyanophenyl)isoxazolin-5(S)-ylacetic acid (127 g, 0.55 moles) and (+)-cinchonidine (180.37 g, 0.55 mol) were added to acetone (2.0 L) and stirred at ambien temperature for at least 1.5 hrs. The resulting precipitate (169.21 g) was collected by filtration. The precipitate was dissolved in hot acetone (4.0 L) while stirring. After complete dissolution, the solution was allowed to stand overnight. The crystals formed were collected by filtration and recrystallized with acetone again to yield the 3-(4-cyanophenyl)isoxazolin-5(S)-ylacetic acid / (+)-cinchonidine salt in 33% overall yield and >99 % diastereomeric excess. The 3-(4-cyanophenyl)isoxazolin-5(S)-ylacetic acid was liberated from its cinchonidine salt complex by suspending the salt in ethereal HCL (1 N), filtering the solid after equilibration and evaporating the ether solution to provide the solid 3-(4-cyanophenyl)isoxazolin-5(S)-ylacetic acid. The R-isomer

could be obtained from the mother liquor. Other chiral bases used include ephedrine, 2-phenylglycinol, 2-amino-3-methoxy-1-propanol, quinidine and pseudoephedrine.

Example 2503

General Procedure for the Preparation of Compounds of the Formula (Ie) and (If).

Part A. Z-2,3-diaminopropionic acid (2.5 g, Fluka) was combined with Fmoc-N-Hydroxysuccinimide (1.1 eq., 3.89 g) and $NaHCO_3$ (3 eq., 2.65 g), in dioxane (24 ml) and H_2O (21 ml). After stirring at room temperature overnight, the pH was adjusted with Na_2CO_3 to pH 9. The solution was extracted three times with ethyl ether, then the aqueous layer was acidified with conc. HCl, with stirring. At pH 4-5, a solid precipitated out. This was filtered, rinsed with 1 N HCl, and dried. (93% yield)

Part B. Wang resin (2.0 g, 1.16 mmole/g, Advanced Chem Tech) was added to triphenylphosphine (5 eq, 3.0 g) in 20 ml DMF. CBr_4 (5 eq, 3.85 g) was then added and the solution was stirred at room temperature 3 hours. The resin was filtered and rinsed with DMF. Fmoc-Z-2,3-diaminopropionic acid (1.60 g, 1.5 equiv.) was dissolved in 20 ml DMF and the above resin was added, with 1.5 equiv. DIEA (0.60 ml) and 1.0 equiv. CsI (0.60 g) and stirred at room temperature overnight. The resin was filtered and rinsed with DMF and MeOH. Weight gain, IR, elemental analysis, and picric acid determination were used to establish the substitution level of the resin as approx. 0.8 mmole/g.

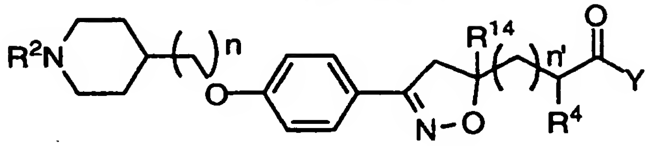
Part C. The above derivatized resin (150 mg) was deprotected by mixing 10 min. with 20% piperidine/DMF. of The Fmoc-isoxazolin derivative (1.5 eq., 0.18 mmole) was dissolved in 1.5 ml DMF and added to the resin with HBTU (1.5 eq, 68 mg) and DIEA (1.5 eq, 32 ul). The tubes

were mixed overnight, then drained, rinsed with DMF and MeOH, and the resin split into two portions. One portion was deprotected with 20% piperidine/DMF and then cleaved to produce the primary amine analogs. The other portion was deprotected with 20% piperidine/DMF and then coupled overnight with bis Boc-S-ethyl isothiourea (2 eq., 37 mg) and DEA (2 eq., 21 ul) in DMF.

Part D. After rinsing, the compounds were cleaved from the resin by mixing with 1: 1 TFA:CH_2Cl_2 for two hours. The filtrate was rotovapped under reduced pressure to an oil, dissolved in 1: 1 acetonitrile:H_2O, and lyophilized. The crude material was analyzed by mass spec and HPLC. They were then purified by reverse phase HPLC (ACN:H_2O:0.1 % TFA, C 18 column).

Using the above methods and variations thereof known in the art of organic synthesis, the additional examples in Tables 1-2, 2A-2D, 3-14 can be prepared.

Table 1



(V)

Ex. No.	R^2	R^4	Y	n	R^{14}	n'
1	H	H	OH	2	H	0
2	H	$NHSO_2nC_4H_9$	OH	2	H	0
3	H	$NHSO_2CH_2Ph$	OH	2	H	0
4	H	$NHCO_2CH_2Ph$	OH	2	H	0
5	H	$NHCOnC_4H_9$	OH	2	H	0
6	H	H	OH	1	H	1
7	H	H	OH	1	H	0
8	H	H	OH	2	H	1
9	H	$NHSO_2nC_4H_9$	OH	1	H	1
10	H	$NHSO_2CH_2Ph$	OH	1	H	1
11	H	$NHCO_2CH_2Ph$	OH	1	H	1
12	H	$NHCOnC_4H_9$	OH	1	H	1
13	H	$NHSO_2nC_4H_9$	OMe	2	H	0
14	H	$NHCO_2CH_2Ph$	OMe	2	H	0
15	H	$NHSO_2nC_4H_9$	OMe	1	H	1
16	H	$NHCO_2CH_2Ph$	OMe	1	H	1
17	H	$NHSO_2nC_4H_9$	OEt	2	H	0
18	H	$NHCO_2CH_2Ph$	OEt	2	H	0
19	H	$NHSO_2nC_4H_9$	OEt	1	H	1
20	H	$NHCO_2CH_2Ph$	OEt	1	H	1
21	Boc	$NHSO_2nC_4H_9$	OH	2	H	0
22	Boc	$NHCO_2CH_2Ph$	OH	2	H	0
23	Boc	$NHSO_2nC_4H_9$	OH	1	H	1
24	Boc	$NHCO_2CH_2Ph$	OH	1	H	1
25	Cbz	$NHSO_2nC_4H_9$	OH	2	H	0
26	Cbz	$NHCO_2CH_2Ph$	OH	2	H	0
27	Cbz	$NHSO_2nC_4H_9$	OH	1	H	1
Ex. No.	R^2	R^4	Y	n	R^{14}	n'

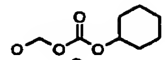
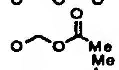
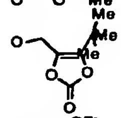
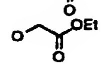
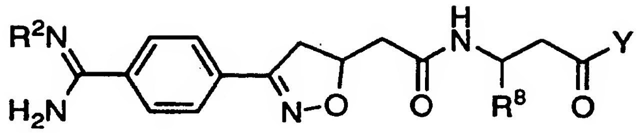
28	Cbz	$NHCO_2CH_2Ph$	OH	1	H	1
29	H	$NHSO_2nC_4H_9$		2	H	0
30	H	$NHSO_2nC_4H_9$		2	H	0
31	H	$NHSO_2nC_4H_9$		2	H	0
32	H	$NHSO_2nC_4H_9$		2	H	0
31	H	$NHSO_2nC_4H_9$		2	H	0
33	H	H	OH	2	CO_2Me	0
34	H	H	OMe	2	H	0
35	H	$NHSO_2CH_2Ph$	OMe	2	H	0
36	H	$NHCOnC_4H_9$	OMe	2	H	0
37	H	H	OMe	1	H	1
38	H	H	OMe	1	H	0
39	H	H	OMe	2	H	1
40	H	$NHSO_2CH_2Ph$	OMe	1	H	1
41	H	$NHCOnC_4H_9$	OMe	1	H	1
42	H	H	OMe	2	CO_2Me	0

Table 2



(VI)

Example Number	R^2	R^8	Y	MS $(M+H)^+$
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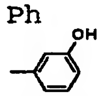
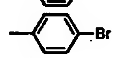
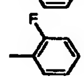
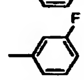
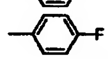
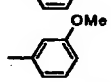
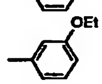
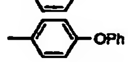
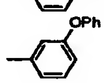
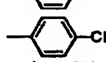
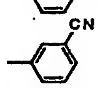
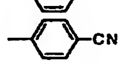
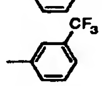
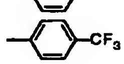
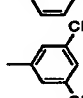
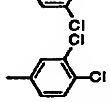
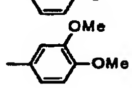
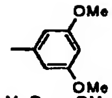
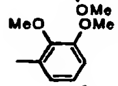
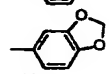
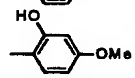
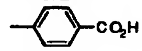
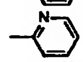
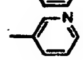
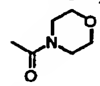
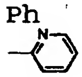
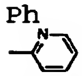
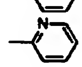
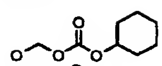
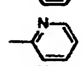
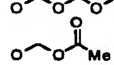
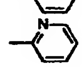
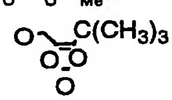
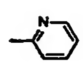
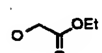
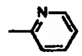
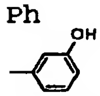
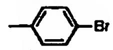
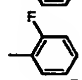
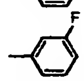
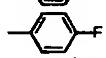
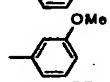
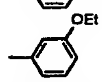
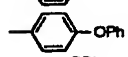
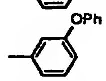
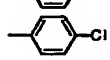
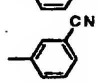
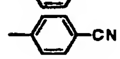
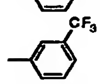
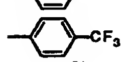
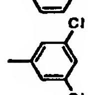
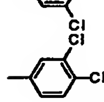
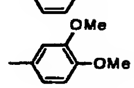
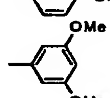
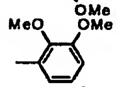
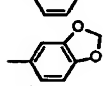
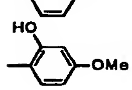
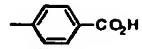
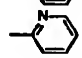
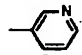
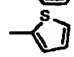
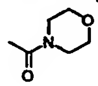
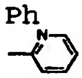
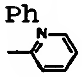
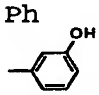
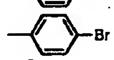
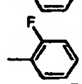
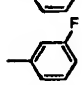
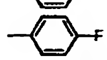
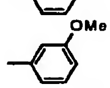
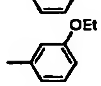
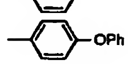
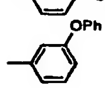
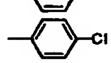
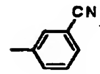
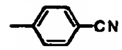
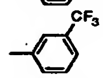
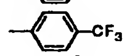
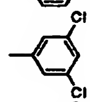
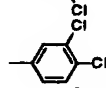
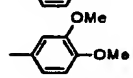
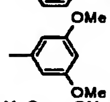
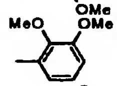
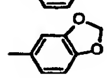
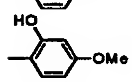
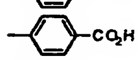
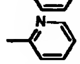
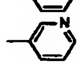
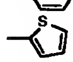
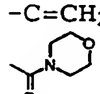
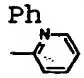
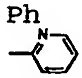
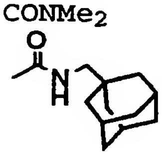
43A	H	Ph	OH	HNMR
44	H		OH	
45	H		OH	
46	H		OH	
47	H		OH	
48	H		OH	
49	H		OH	
50	H		OH	
51	H		OH	
52	H		OH	
53	H		OH	
54	H		OH	
55	H		OH	
56	H		OH	
57	H		OH	
58	H		OH	
59	H		OH	
60	H		OH	

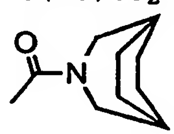
Example Number	R^2	R^8	Y	MS $(M+H)^+$
61	H		OH	
62	H		OH	
63	H		OH	
64	H		OH	
65	H		OH	
66	H		OH	
67	H		OH	
68	H		OH	
69	H	Et	OH	
70	H	*n*-Pr	OH	
71	H	-C≡CH	OH	
72	H	CO_2H	OH	
73	H	CH_2Ph	OH	
74	H	CH_2CH_2Ph	OH	
75	H	$-C{=}CH_2$	OH	
76	H		OH	
80	Cbz	Ph	OH	
81	Cbz		OH	
82	Boc	Ph	OH	
83	Boc		OH	
84	H			
85	H			
86	H			
87	H			

Example Number	R^2	R^8	Y	MS $(M+H)^+$
88	H			
89	H	Ph	OMe	
90	H		OMe	
91	H		OMe	
92	H		OMe	
93	H		OMe	
94	H		OMe	
95	H		OMe	
96	H		OMe	
97	H		OMe	
98	H		OMe	
99	H		OMe	
100	H		OMe	
101	H		OMe	
102	H		OMe	
103	H		OMe	
104	H		OMe	
105	H		OMe	
106	H		OMe	
107	H		OMe	
108	H		OMe	
109	H		OMe	
110	H		OMe	

Example Number	R^2	R^8	Y	MS $(M+H)^+$
111	H		OMe	
112	H		OMe	
113	H		OMe	
114	H		OMe	
115	H	Et	OMe	361
116	H	*n*-Pr	OMe	
117	H	-C≡CH	OMe	
118	H	CO_2H	OMe	
119	H	CH_2Ph	OMe	423
120	H	CH_2CH_2Ph	OMe	437
121	H	$-C{=}CH_2$	OMe	
122	H		OMe	
126	Cbz	Ph	OMe	
127	Cbz		OMe	
128	Boc	Ph	OMe	
129	Boc		OMe	
130	H	Ph	OEt	
131	H		OEt	
132	H		OEt	
133	H		OEt	
134	H		OEt	
135	H		OEt	
136	H		OEt	
137	H		OEt	
138	H		OEt	
139	H		OEt	
140	H		OEt	

Example Number	R^2	R^8	Y	MS $(M+H)^+$
141	H		OEt	
142	H		OEt	
143	H		OEt	
144	H		OEt	
145	H		OEt	
146	H		OEt	
147	H		OEt	
148	H		OEt	
149	H		OEt	
150	H		OEt	
151	H		OEt	
152	H		OEt	
153	H		OEt	
154	H		OEt	
155	H		OEt	
156	H	Et	OEt	
157	H	*n*-Pr	OEt	
158	H	-C≡CH	OEt	
159	H	CO_2H	OEt	
160	H	CH_2Ph	OEt	
161	H	CH_2CH_2Ph	OEt	
162	H	$-C=CH_2$	OEt	
163	H		OEt	
164	H	$CH_2N(Me)Ph$	OEt	
165	H	CH_2NEt_2	OEt	
166	H	CH_2NMe_2	OEt	

Example Number	R^2	R^8	Y	MS $(M+H)^+$
167	Cbz	Ph	OEt	
168	Cbz		OEt	
169	Boc	Ph	OEt	
170	Boc		OEt	
338	H	CO_2Me	OMe	mp 160°
339	H	CO_2Me	H	363
340	H	$CONMe_2$	OMe	404
341	H		OMe	524
343	H	n-butyl	OH	
344	H	n-butyl	OMe	389
345	H	n-butyl	OEt	
346	H	isobutyl	OH	
347	H	isobutyl	OMe	389
348	H	isobutyl	OEt	403
349	H	CH_2SPh	OH	
350	H	CH_2SPh	OMe	455
351	H	CH_2SPh	OEt	
352	H	CH_2OPh	OH	
353	H	CH_2OPh	OMe	
354	H	CH_2OPh	OEt	
355	H	CH_2SO_2Ph	OH	
356	H	CH_2SO_2Ph	OMe	
357	H	CH_2SO_2Ph	OEt	
358	H	CH_2NHSO_2Ph	OH	
359	H	CH_2NHSO_2Ph	OMe	502
360	H	CH_2NHSO_2Ph	OEt	
361	H	$CH_2NHSO_2n\text{-}Bu$	OH	
362	H	$CH_2NHSO_2n\text{-}Bu$	OMe	482
363	H	$CH_2NHSO_2n\text{-}Bu$	OEt	
364	H	CH_2COOH	OH	377
365	H	CH_2COOMe	OMe	405

Example Number	R^2	R^8	Y	MS $(M+H)^+$
366	H	CH_2COOEt	OEt	
367	H	CH_2CH_2COOH	OH	
368	H	CH_2CH_2COOMe	OMe	419
369	H	CH_2CH_2COOEt	OEt	
370	H	CH_2NMe_2	OH	
371	H	CH_2NMe_2	OMe	390
372	H	CH_2NMe_2	OEt	
434	BOC	$-C(=O)NH-(CH_2)_2C_6H_5$	OtBu	622
435	H	$-C(=O)NH-(CH_2)_2C_6H_5$	OH	466
439	H	$-C(=O)OC_2H_5$	OEt	419
441	H		OH	484
446	H	$(CH_2)_3Ph$	OMe	
447	H	$CH_2-(2\text{-pyr})$	OMe	
448	H	$(CH_2)_2-(2\text{-pyr})$	OMe	
449	H	$(CH_2)_2-(3\text{-pyr})$	OMe	438
450	H	$(CH_2)_2-(4\text{-pyr})$	OMe	438
452	H	$-C(=O)NH-(CH_2)_2C_6H_5$	OMe	480
453	BOC	$C(O)\cdot N \quad N\cdot CH_2Ph$	OMe	635
454	H	$C(=O)N(CH_3)-(CH_2)_2C_6H_5$	OMe	
455	H	$C(O)\cdot N \quad N\cdot CH_2Ph$	OMe	
456	H	i-hexyl	OEt	431
457	H	$-C{\equiv}CSiMe_3$	OMe	429
458	H	$-(CH_2)_2-(3\text{-pyr})$	OH	424
459	H	$-(CH_2)_2-(2\text{-pyr})$	OH	424
460	H	$-(CH_2)_3-C_6H_5$	OH	437

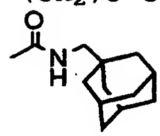
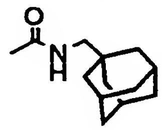
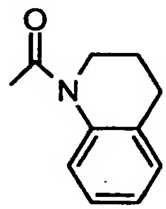
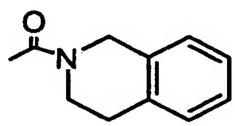
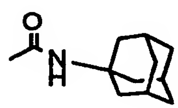
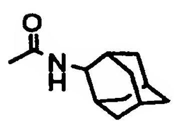
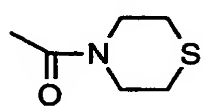
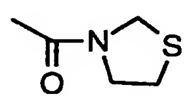
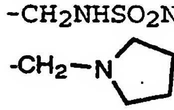
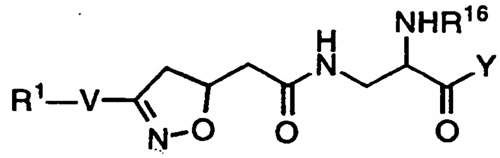
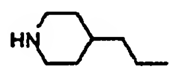
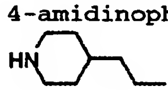
Example Number	R^2	R^8	Y	MS $(M+H)^+$
461	H	$-(CH_2)3-C_6H_5$	OMe	451
462	H		OEt	538
463	H		OH	510
464	H		OMe	492
465	H		OMe	492
466	H		OMe	510
467	H		OMe	510
468	H		OMe	462
469	H		OMe	448
587	H	$-(CH_2)_3-$(4-pyr)	OH	424
611	H	$-CH_2NHSO_2NMe_2$	OMe	469
612	H		OMe	416

Table 2A



Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
275	4-amidinophenyl	H	OH	334
276	4-amidinophenyl	benzyloxycarbonyl	OH	468
277	4-amidinophenyl	t-butyloxycarbonyl	OH	
278	4-amidinophenyl	n-butyloxycarbonyl	OH	434
278a	4-amidinophenyl	n-butyloxycarbonyl	OMe	448
278b	4-amidinophenyl	n-butyloxycarbonyl	OH	434
279	4-amidinophenyl	ethyloxycarbonyl	OH	
280	4-amidinophenyl	methyloxycarbonyl	OH	
290	4-amidinophenyl	phenylethylcarbonyl	OH	510
291	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OH	
292	4-amidinophenyl	n-pentylcarbonyl	OH	
293	4-amidinophenyl	n-butylcarbonyl	OH	
294	4-amidinophenyl	propionyl	OH	
295	4-amidinophenyl	acetyl	OH	
296	4-amidinophenyl	methylsulfonyl	OH	
297	4-amidinophenyl	ethylsulfonyl	OH	
298	4-amidinophenyl	n-butylsulfonyl	OH	
299	4-amidinophenyl	phenylsulfonyl	OH	474
300	4-amidinophenyl	4-methylphenyl-sulfonyl	OH	488
301	4-amidinophenyl	benzylsulfonyl	OH	
302	4-amidinophenyl	2-pyridylcarbonyl	OH	
303	4-amidinophenyl	3-pyridylcarbonyl	OH	
304	4-amidinophenyl	4-pyridylcarbonyl	OH	
305	4-amidinophenyl	2-pyridylmethyl-carbonyl	OH	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
306	4-amidinophenyl	3-pyridylmethyl-carbonyl	OH	
307	4-amidinophenyl	4-pyridylmethyl-carbonyl	OH	
308	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OH	
309	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OH	
310	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OH	
311	4-amidinophenyl	H	OMe	
312	4-amidinophenyl	benzyloxycarbonyl	OMe	482
313	4-amidinophenyl	t-butyloxycarbonyl	OMe	
314	4-amidinophenyl	n-butyloxycarbonyl	OMe	448
315	4-amidinophenyl	ethyloxycarbonyl	OMe	
316	4-amidinophenyl	methyloxycarbonyl	OMe	
317	4-amidinophenyl	phenylethylsulfonyl	OH	502
318	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OMe	
319	4-amidinophenyl	n-pentylcarbonyl	OMe	
320	4-amidinophenyl	n-butylcarbonyl	OMe	
321	4-amidinophenyl	propionyl	OMe	
322	4-amidinophenyl	acetyl	OMe	
323	4-amidinophenyl	methylsulfonyl	OMe	426
324	4-amidinophenyl	ethylsulfonyl	OMe	440
325	4-amidinophenyl	n-butylsulfonyl	OMe	
326	4-amidinophenyl	phenylsulfonyl	OMe	488
327	4-amidinophenyl	4-methylphenyl-sulfonyl	OMe	502
328	4-amidinophenyl	benzylsulfonyl	OMe	502
329	4-amidinophenyl	2-pyridylcarbonyl	OMe	
330	4-amidinophenyl	3-pyridylcarbonyl	OMe	
331	4-amidinophenyl	4-pyridylcarbonyl	OMe	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
332	4-amidinophenyl	2-pyridylmethyl-carbonyl	OMe	
333	4-amidinophenyl	3-pyridylmethyl-carbonyl	OMe	
334	4-amidinophenyl	4-pyridylmethyl-carbonyl	OMe	
335	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OMe	
336	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OMe	
337	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OMe	
374		benzyloxycarbonyl	OMe	475
440	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	582
442	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	594
443	4-amidinophenyl	1-naphthylsulfonyl	OMe	538
444	4-amidinophenyl	2-naphthylsulfonyl	OMe	538
445	4-amidinophenyl	styrylsulfonyl	OMe	514
445a	4-amidinophenyl	styrylsulfonyl	OH	500
451		n-butyloxycarbonyl	OMe	441
471	4-amidinophenyl	4-butyloxyphenyl-sulfonyl	OMe	560
472	4-amidinophenyl	2-thienylsulfonyl	OMe	494
473	4-amidinophenyl	3-methylphenyl-sulfonyl	OMe	502
474	4-amidinophenyl	4-iodophenyl	OMe	614
475	4-amidinophenyl	3-trifluoromethyl-phenylsulfonyl	OMe	556
476	4-amidinophenyl	3-chlorophenyl-sulfonyl	OMe	522
477	4-amidinophenyl	2-methoxycarbonyl-phenylsulfonyl	OMe	546

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
478	4-amidinophenyl	2,4,6-trimethyl-phenylsulfonyl	OMe	530
478a	4-amidinophenyl	2,4,6-trimethyl-phenylsulfonyl	OH	516
479	4-amidinophenyl	2-chlorophenyl-sulfonyl	OMe	522
479a	4-amidinophenyl	2-chlorophenyl-sulfonyl	OH	508
480	4-amidinophenyl	2-trifluoromethyl-phenylsulfonyl	OMe	556
481	4-amidinophenyl	4-trifluoromethyl-phenylsulfonyl	OMe	556
482	4-amidinophenyl	2-fluorophenyl-sulfonyl	OMe	506
483	4-amidinophenyl	4-fluorophenyl-sulfonyl	OMe	506
484	4-amidinophenyl	4-methoxyphenyl-sulfonyl	OMe	518
485	4-amidinophenyl	2,3,5,6-tetramethyl-phenylsulfonyl	OMe	544
485a	4-amidinophenyl	2,3,5,6-tetramethyl-phenylsulfonyl	OH	530
486	4-amidinophenyl	4-cyanophenyl-sulfonyl	OMe	513
487	4-amidinophenyl	4-chlorophenyl-sulfonyl	OMe	522
488	4-amidinophenyl	4-ethylphenyl-sulfonyl	OMe	516
489	4-amidinophenyl	4-propylphenyl-sulfonyl	OMe	530
490	4-amidinophenyl	n-propylsulfonyl	OMe	454
490a	4-amidinophenyl	n-propylsulfonyl	OH	440
491	4-amidinophenyl	2-phenylethyl-sulfonyl	OMe	516

492	4-amidinophenyl	4-isopropylphenyl-sulfonyl	OMe	530
492a	4-amidinophenyl	4-isopropylphenyl-sulfonyl	OH	516
493	4-amidinophenyl	3-phenylpropyl-sulfonyl	OMe	530
494	4-amidinophenyl	3-pyridylsulfonyl	OMe	489

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
495	4-amidinophenyl	2-pyridylsulfonyl	OMe	489
496	4-amidinophenyl	2,2-diphenyl-1-ethenylsulfonyl	OMe	590
497	4-amidinophenyl	2-pyrimidinyl-sulfonyl	OMe	
498	4-amidinophenyl	4-methyl-2-pyrimidinylsulfonyl	OMe	
499	4-amidinophenyl	4,6-dimethyl-2-pyrimidinylsulfonyl	OMe	
500	4-amidinophenyl	1,2,4-triazol-3-ylsulfonyl	OMe	
501	4-amidinophenyl	1-methyl-1,3,4-triazol-5-ylsulfonyl	OMe	
502	4-amidinophenyl	3,5-dimethyl-4-pyrazolylsulfonyl	OMe	
503	4-amidinophenyl	1-phenyl-4-pyrazolylsulfonyl	OMe	
504	4-amidinophenyl	n-butylaminosulfonyl	OMe	483
505	4-amidinophenyl	i-butylaminosulfonyl	OMe	483
506	4-amidinophenyl	t-butylaminosulfonyl	OMe	483
507	4-amidinophenyl	i-propylamino-sulfonyl	OMe	469
508	4-amidinophenyl	cyclohexylamino-sulfonyl	OMe	509
509	4-amidinophenyl	phenylaminosulfonyl	OMe	503
510	4-amidinophenyl	benzylaminosulfonyl	OMe	517

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
511	4-amidinophenyl	dimethylamino-sulfonyl	OMe	455
512	4-amidino-2-fluoro-phenyl	3-methylphenyl-sulfonyl	OMe	520
512A	4-amidino-2-fluoro-phenyl	3-methylphenylsulfonyl	OH	506
514	2-amidino-5-pyridyl	3-methylphenyl-sulfonyl	OMe	503
514A	2-amidino-5-pyridyl	3-methylphenylsulfonyl	OH	489
516	3-amidino-6-pyridyl	3-methylphenyl-sulfonyl	OMe	503
516A	3-amidino-6-pyridyl	3-methylphenylsulfonyl	OH	489
518	4-amidinophenyl	4-fluorophenylamino-carbonyl	OMe	485
519	4-amidinophenyl	1-naphthylamino-carbonyl	OMe	517
520	4-amidinophenyl	benzylaminocarbonyl	OMe	
521	4-amidinophenyl	n-butylaminocarbonyl	OMe	435
522	4-amidinophenyl	4-ethylphenyl-carbonyl	OMe	480
523	4-amidinophenyl	biphenylcarbonyl	OMe	528
524	4-amidinophenyl	2-naphthylcarbonyl	OMe	502
525	4-amidinophenyl	(2-chlorophenyl) methoxycarbonyl	OMe	516
526	4-amidinophenyl	(2-chlorophenyl) methoxycarbonyl	OH	502
527	4-amidinophenyl	(2-bromophenyl) methoxycarbonyl	OMe	562
528	4-amidinophenyl	(2-bromophenyl) methoxycarbonyl	OH	548
528a	4-amidinophenyl	(2-bromophenyl)-carbonyl	OH	516
529	4-amidinophenyl	n-hexyloxycarbonyl	OMe	476
530	4-amidinophenyl	n-hexyloxycarbonyl	OH	460

531	4-amidinophenyl	isobutyloxycarbonyl	OMe	448
532	4-amidinophenyl	isobutyloxycarbonyl	OH	434
533	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OMe	460
534	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OH	446
Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
535	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OMe	488
536	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OH	474
537	4-amidinophenyl	4,4,4-trifluoro-butyloxycarbonyl	OMe	502
538	4-amidinophenyl	4,4,4-trifluoro-butyloxycarbonyl	OH	488
539	4-amidinophenyl	n-propylsulfonyl	OMe	
540	4-amidinophenyl	2-methylphenyl-carbonyl	OH	452
540a	4-amidinophenyl	2-methylphenyl-sulfonyl	OH	488
541	4-amidinophenyl	4-chloro-2,5-dimethyl-phenylsulfonyl	OMe	550
541a	4-amidinophenyl	4-chloro-2,5-dimethyl-phenylsulfonyl	OMe	536
542	4-amidinophenyl	2,3-dichlorophenyl-sulfonyl	OMe	556
543	4-amidinophenyl	2-bromophenyl-sulfonyl	OMe	568
544	4-amidinophenyl	3-bromophenyl-sulfonyl	OMe	568
545	4-amidinophenyl	4-bromophenyl-sulfonyl	OMe	568
546	4-amidinophenyl	biphenylsulfonyl	OMe	564
547	4-amidinophenyl	5-chloro-1,3-dimethyl-4-pyrazolyl	OMe	540

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
548	4-amidinophenyl	3-bromo-2-thienylsulfonyl	OMe	574
549	4-amidinophenyl	5-bromo-2-thienylsulfonyl	OMe	574
550	4-amidinophenyl	5-[1-methyl-5-trifluoromethyl-3-pyrazolyl]-2-thienylsulfonyl	OMe	642
551	4-amidinophenyl	5-(3-isoxazolyl)-2-thienylsulfonyl	OMe	561
552	4-amidinophenyl	5-(2-pyridinyl)-2-thienylsulfonyl	OMe	571
553	4-amidinophenyl	4-methyl-2-methylcarbonylamino-5-thiazolylsulfonyl	OMe	566
554	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	628
555	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	544
556	4-amidinophenyl	3-methyl-2-benzothienylsulfonyl	OMe	558
557	4-amidinophenyl	8-quinolinylsulfonyl	OMe	539
558	4-amidinophenyl	8-quinolinylsulfonyl	OH	525
559	4-amidinophenyl	2,1,3-benzo-thiadiazol-4-ylsulfonyl	OMe	546
560	4-amidinophenyl	2,1,3-benzo-thiadiazol-4-ylsulfonyl	OH	532
561	4-amidinophenyl	4-N,N-dimethylamino-1-naphthylsulfonyl	OMe	
562	4-amidinophenyl	4-N,N-dimethylamino-1-haphthylsulfonyl	OH	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
563	4-amidinophenyl	2,1,3-benzoxadiazol-4-ylsulfonyl	OMe	
564	4-amidinophenyl	2,1,3-benzoxadiazol-4-ylsulfonyl	OH	
565	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OMe	
566	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OH	
567	4-N-methylamidino phenyl	3-methylphenylsulfonyl	OMe	
568	4-N-ethylamidino phenyl	3-methylphenylsulfonyl	OMe	530
569	4-N-n-propylamidino phenyl	3-methylphenylsulfonyl	OMe	
570	4-N-benzylamidino phenyl	3-methylphenylsulfonyl	OMe	
571	4-N-n-butylamidino phenyl	3-methylphenylsulfonyl	OMe	558
572	4-N-methylamidino phenyl	3-methylphenylsulfonyl	OH	
573	4-N-ethylamidino phenyl	3-methylphenylsulfonyl	OH	516
574	4-N-n-propylamidino phenyl	3-methylphenylsulfonyl	OH	
575	4-N-benzylamidino phenyl	3-methylphenylsulfonyl	OH	
576	4-N-n-butylamidino phenyl	3-methylphenylsulfonyl	OH	544
577	4-N-methylamidino-phenyl	n-butyloxycarbonyl	OMe	
578	4-N-ethylamidinophenyl	n-butyloxycarbonyl	OMe	
579	4-N-npropylamidino-phenyl	n-butyloxycarbonyl	OMe	

580	4-N-n-butylamidino-phenyl	n-butyloxycarbonyl	OMe	504
581	4-N-benzylamidino-phenyl	n-butyloxycarbonyl	OMe	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
582	4-N-methylamidino-phenyl	n-butyloxycarbonyl	OH	
583	4-N-ethylamidino-phenyl	n-butyloxycarbonyl	OH	
584	4-N-n-propylamidino-phenyl	n-butyloxycarbonyl	OH	
585	4-N-n-butylamidino-phenyl	n-butyloxycarbonyl	OH	
586	4-N-benzylamidino-phenyl	n-butyloxycarbonyl	OH	
589	4-(acetoxyamidino)-phenyl	n-butyloxycarbonyl	OMe	
590	4-(acetoxyamidino)-phenyl	n-butyloxycarbonyl	OH	
591	4-(acetoxyamidino)-phenyl	isobutyloxycarbonyl	OMe	
592	4-(acetoxyamidino)-phenyl	isobutyloxycarbonyl	OH	
593	4-(acetoxyamidino)-phenyl	cyclopropylethoxy-carbonyl	OMe	
594	4-(acetoxyamidino)-phenyl	cyclopropylethoxy-carbonyl	OH	
595	4-(acetoxyamidino)-phenyl	benzyloxycarbonyl	OMe	
596	4-(acetoxyamidino)-phenyl	benzyloxycarbonyl	OH	
597	4-(acetoxyamidino)-phenyl	4-methylphenylsulfonyl	OMe	
598	4-(acetoxyamidino)-phenyl	4-methylphenylsulfonyl	OH	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
599	4-(acetoxyamidino)-phenyl	3-methylphenylsulfonyl	OMe	
600	4-(acetoxyamidino)-phenyl	3-methylphenylsulfonyl	OH	
601	4-guanidinophenyl	n-butyloxycarbonyl	OH	
602	4-guanidinophenyl	n-butyloxycarbonyl	OMe	463
603	4-guanidinophenyl	benzyloxycarbonyl	OH	
604	4-guanidinophenyl	benzyloxycarbonyl	OMe	
605	4-guanidinophenyl	4-methylphenylsulfonyl	OH	503
606	4-guanidinophenyl	4-methylphenylsulfonyl	OMe	517
607	4-guanidinophenyl	3-methylphenylsulfonyl	OH	
608	4-guanidinophenyl	3-methylphenylsulfonyl	OMe	
609	4-guanidinophenyl	n-butylsulfonyl	OH	
610	4-guanidinophenyl	n-butylsulfonyl	OMe	
613	4-amidino-2-fluoro-phenyl	n-butyloxycarbonyl	OMe	466
614	4-piperidinyl	n-butyloxycarbonyl	OMe	412
615	4-piperidinylmethyl	n-butyloxycarbonyl	OMe	426
616	4-piperidinylpropyl	n-butyloxycarbonyl	OMe	454
617	4-quanidinophenyl	n-butyloxycarbonyl	OH	449
618	4-amidinophenylmethyl	benzyloxycarbonyl	OMe	
619	4-amidinophenylmethyl	benzyloxycarbonyl	OH	
220	4-amidinophenylmethyl	n-butyloxycarbonyl	OMe	
621	4-amidinophenylmethyl	n-butyloxycarbonyl	OH	
622	4-amidinophenylmethyl	cyclopropylethoxy carbonyl	OMe	
623	4-amidinophenylmethyl	cyclopropylethoxy carbonyl	OH	
624	4-amidinophenylmethyl	4-methylphenylsulfonyl	OMe	
625	4-amidinophenylmethyl	4-methylphenylsulfonyl	OH	488
626	4-amidinophenylmethyl	3-methylphenylsulfonyl	OMe	
627	4-amidinophenylmethyl	3-methylphenylsulfonyl	OH	

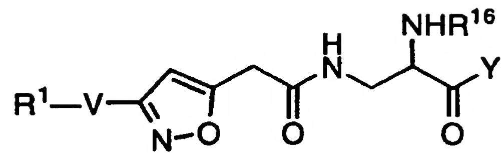
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
628	4-amidinophenylmethyl	n-butylsulfonyl	OMe	
629	4-amidinophenylmethyl	n-butylsulfonyl	OH	
630	4-amidinophenylmethoxy	benzyloxycarbonyl	OMe	
631	4-amidinophenylmethoxy	benzyloxycarbonyl	OH	
632	4-amidinophenylmethoxy	n-butyloxycarbonyl	OMe	
633	4-amidinophenylmethoxy	n-butyloxycarbonyl	OH	
634	4-amidinophenylmethoxy	cyclopropylethoxy carbonyl	OMe	
635	4-amidinophenylmethoxy	cyclopropylethoxy carbonyl	OH	
636	4-amidinophenylmethoxy	4-methylphenylsulfonyl	OMe	
637	4-amidinophenylmethoxy	4-methylphenylsulfonyl	OH	
638	4-amidinophenylmethoxy	3-methylphenylsulfonyl	OMe	
639	4-amidinophenylmethoxy	3-methylphenylsulfonyl	OH	
640	4-amidinophenylmethoxy	n-butylsulfonyl	OMe	
641	4-amidinophenylmethoxy	n-butylsulfonyl	OH	
642	4-amidinophenyl	5-chloro-1,3-dimethyl-4-pyrazolyl	OMe	526
643	4-amidinophenyl	1-methylimidazol-4-ylsulfonyl	OH	478
644	4-amidinophenyl	3,5-dimethyl-1,3-thioimidazole-2-ylsulfonyl	OH	509
645	N-t-butyloxycarbonyl-4-amidinophenyl	5-(2-pyridinyl)-2-thienylsulfonyl	OMe	671
646	N-t-butyloxycarbonyl-4-amidinophenyl	3,5-dimethyl-1,3-thioimidazole-2-ylsulfonyl	OMe	623
647	N-t-butyloxycarbonyl-4-amidinophenyl TFA salt, 5(R),N^2(S) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OMe	607

1293	guanidinopropyl	2-benzothiophene-sulfonyl	OMe	
1294	guanidinopropyl	n-butyloxycarbonyl	OH	
1295	guanidinopropyl	n-propyloxycarbonyl	OH	
1296	guanidinopropyl	benzyloxycarbonyl	OH	
1297	guanidinopropyl	n-butylsulfonyl	OH	
1298	guanidinopropyl	2-methylphenyl-sulfonyl	OH	
1299	guanidinopropyl	3-methylphenyl-sulfonyl	OH	
1300	guanidinopropyl	4-methylphenyl-sulfonyl	OH	
1301	guanidinopropyl	2-bromophenylsulfonyl	OH	
1302	guanidinopropyl	3-bromophenylsulfonyl	OH	
1303	guanidinopropyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1304	guanidinopropyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1305	guanidinopropyl	benzylsulfonyl	OH	
1306	guanidinopropyl	styrylsulfonyl	OH	
1307	guanidinopropyl	2-benzothiophene-sulfonyl	OH	
1308	guanidinobutyl	n-butyloxycarbonyl	OH	
1309	guanidinobutyl	n-butylsulfonyl	OH	
1310	guanidinobutyl	phenylsulfonyl	OH	
1311	guanidinobutyl	2-methylphenyl-sulfonyl	OH	
1312	guanidinobutyl	4-methylphenyl-sulfonyl	OH	
1313	guanidinobutyl	2-bromophenylsulfonyl	OH	
1314	guanidinobutyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1315	guanidinobutyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1316	guanidinobutyl	benzylsulfonyl	OH	
1317	guanidinobutyl	styrylsulfonyl	OH	
1318	guanidinobutyl	3-fluorophenyl-sulfonyl	OH	
1319	guanidinobutyl	n-butyloxycarbonyl	OMe	
1320	guanidinobutyl	n-butylsulfonyl	OMe	
1321	guanidinobutyl	benzyloxycarbonyl	OH	449
1322	guanidinobutyl	phenylsulfonyl	OMe	
1323	guanidinobutyl	2-methylphenyl-sulfonyl	OMe	
1324	guanidinobutyl	2-bromophenylsulfonyl	OMe	
1325	guanidinobutyl	3-bromophenylsulfonyl	OMe	
1326	guanidinobutyl	3,5-dimethyl-isoxazolyl sufonyl	OMe	
1327	guanidinobutyl	benzylsulfonyl	OMe	
1328	guanidinobutyl	n-butyloxycarbonyl	OH	
1329	guanidinobutyl	isobutyloxycarbonyl	OH	
1330	guanidinobutyl	n-propyloxycarbonyl	OH	
1331	guanidinobutyl	phenylsulfonyl	OH	
1332	guanidinobutyl	n-butylsulfonyl	OH	
1333	guanidinobutyl	2-methylphenyl-sulfonyl	OH	
1334	guanidinobutyl	3-methylphenyl-sulfonyl	OH	
1335	guanidinobutyl	4-methylphenyl-sulfonyl	OH	
1336	guanidinobutyl	2-bromophenylsulfonyl	OH	

1256	4-amidino-piperidinylmethyl	n-propylsulfonyl	OMe	
1257	4-amidino-piperidinylmethyl	2-methylphenyl-sulfonyl	OMe	
1258	4-amidino-piperidinylmethyl	3-methylphenyl-sulfonyl	OMe	
1259	4-amidino-piperidinylmethyl	4-methylphenyl-sulfonyl	OMe	
1260	4-amidino-piperidinylmethyl	2-bromophenylsulfonyl	OMe	
1261	4-amidino-piperidinylmethyl	3-bromophenylsulfonyl	OMe	
1262	4-amidino-piperidinylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1263	4-amidino-piperidinylmethyl	4-methylphenyl-sulfonyl	OH	
1264	4-amidino-piperidinylmethyl	n-butyloxycarbonyl	OH	
1265	4-amidino-piperidinylmethyl	n-propyloxycarbonyl	OH	
1266	4-amidino-piperidinylmethyl	benzyloxycarbonyl	OH	
1267	4-amidino-piperidinylmethyl	n-butylsulfonyl	OH	
1268	4-amidino-piperidinylmethyl	2-methylphenyl-sulfonyl	OH	
1269	4-amidino-piperidinylmethyl	3-methylphenyl-sulfonyl	OH	
1270	4-amidino-piperidinylmethyl	2-bromophenyl-sulfonyl	OH	
1271	4-amidino-piperidinylmethyl	3-bromophenyl-sulfonyl	OH	
1272	4-amidino-piperidinylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1273	4-quinuclidinylethyl	n-butyloxycarbonyl	OH	
1274	4-quinuclidinylethyl	n-propyloxycarbonyl	OH	
1275	4-quinuclidinylethyl	benzyloxycarbonyl	OH	
1276	4-quinuclidinylethyl	n-butylsulfonyl	OH	
1277	4-quinuclidinylethyl	2-methylphenyl-sulfonyl	OH	
1278	4-quinuclidinylethyl	4-methylphenyl-sulfonyl	OH	
1279	4-quinuclidinylethyl	2-bromophenylsulfonyl	OH	
1280	4-quinuclidinylethyl	3-bromophenylsulfonyl	OH	
1281	4-quinuclidinylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1282	guanidinopropyl	n-butyloxycarbonyl	OMe	
1283	guanidinopropyl	n-propyloxycarbonyl	OMe	
1284	guanidinopropyl	benzyloxycarbonyl	OH	435
1285	guanidinopropyl	n-butylsulfonyl	OMe	
1286	guanidinopropyl	2-methylphenyl-sulfonyl	OMe	
1287	guanidinopropyl	3-methylphenyl-sulfonyl	OMe	
1288	guanidinopropyl	2-bromophenylsulfonyl	OMe	
1289	guanidinopropyl	3-bromophenylsulfonyl	OMe	
1290	guanidinopropyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1291	guanidinopropyl	benzylsulfonyl	OMe	
1292	guanidinopropyl	styrylsulfonyl	OMe	

668	4-amidinophenyl	4-methylphenylsulfonyl	methyl	OH
669	4-amidinophenyl	n-butylsulfonyl	methyl	OMe
670	4-amidinophenyl	n-butylsulfonyl	methyl	OH

Table 2D



Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
701	4-amidinophenyl	benzyloxycarbonyl	OH	
702	4-amidinophenyl	t-butyloxycarbonyl	OH	
703	4-amidinophenyl	n-butyloxycarbonyl	OH	
704	4-amidinophenyl	ethyloxycarbonyl	OH	
705	4-amidinophenyl	methyloxycarbonyl	OH	
706	4-amidinophenyl	phenylethylcarbonyl	OH	
707	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OH	
708	4-amidinophenyl	n-pentylcarbonyl	OH	
709	4-amidinophenyl	n-butylcarbonyl	OH	
710	4-amidinophenyl	propionyl	OH	
711	4-amidinophenyl	acetyl	OH	
712	4-amidinophenyl	methylsulfonyl	OH	
713	4-amidinophenyl	ethylsulfonyl	OH	
714	4-amidinophenyl	n-butylsulfonyl	OH	
715	4-amidinophenyl	phenylsulfonyl	OH	
716	4-amidinophenyl	4-methylphenyl-sulfonyl	OH	
717	4-amidinophenyl	benzylsulfonyl	OH	488
718	4-amidinophenyl	2-pyridylcarbonyl	OH	
719	4-amidinophenyl	3-pyridylcarbonyl	OH	
720	4-amidinophenyl	4-pyridylcarbonyl	OH	
721	4-amidinophenyl	2-pyridylmethyl-carbonyl	OH	
722	4-amidinophenyl	3-pyridylmethyl-carbonyl	OH	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
723	4-amidinophenyl	4-pyridylmethyl-carbonyl	OH	
724	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OH	
725	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OH	
726	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OH	
727	4-amidinophenyl	benzyloxycarbonyl	OMe	480
728	4-amidinophenyl	t-butyloxycarbonyl	OMe	
729	4-amidinophenyl	n-butyloxycarbonyl	OMe	446
730	4-amidinophenyl	ethyloxycarbonyl	OMe	
731	4-amidinophenyl	methyloxycarbonyl	OMe	
732	4-amidinophenyl	phenylethylcarbonyl	OMe	
733	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OMe	
734	4-amidinophenyl	n-pentylcarbonyl	OMe	
735	4-amidinophenyl	n-butylcarbonyl	OMe	
736	4-amidinophenyl	propionyl	OMe	
737	4-amidinophenyl	acetyl	OMe	
738	4-amidinophenyl	methylsulfonyl	OMe	
739	4-amidinophenyl	ethylsulfonyl	OMe	
740	4-amidinophenyl	n-butylsulfonyl	OMe	
741	4-amidinophenyl	phenylsulfonyl	OMe	
742	4-amidinophenyl	4-methylphenyl-sulfonyl	OMe	
743	4-amidinophenyl	benzylsulfonyl	OMe	
744	4-amidinophenyl	2-pyridylcarbonyl	OMe	
745	4-amidinophenyl	3-pyridylcarbonyl	OMe	
746	4-amidinophenyl	4-pyridylcarbonyl	OMe	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$

747	4-amidinophenyl	2-pyridylmethyl-carbonyl	OMe	
748	4-amidinophenyl	3-pyridylmethyl-carbonyl	OMe	
749	4-amidinophenyl	4-pyridylmethyl-carbonyl	OMe	
750	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OMe	
751	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OMe	
752	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OMe	
753	4-piperidinylethyl	benzylcarbonyl	OMe	
754	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	
755	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	
756	4-amidinophenyl	1-naphthylsulfonyl	OMe	
757	4-amidinophenyl	2-naphthylsulfonyl	OMe	
758	4-piperidinylethyl	n-butyloxycarbonyl	OMe	440
759	4-amidinophenyl	2-thienylsulfonyl	OMe	
760	4-amidinophenyl	3-methylphenyl-sulfonyl	OMe	
761	4-amidinophenyl	4-fluorophenyl-sulfonyl	OMe	
762	4-amidinophenyl	4-methoxyphenyl-sulfonyl	OMe	
763	4-amidinophenyl	n-propylsulfonyl	OMe	
764	4-amidinophenyl	2-phenylethyl-sulfonyl	OMe	
765	4-amidinophenyl	4-isopropylphenyl-sulfonyl	OMe	

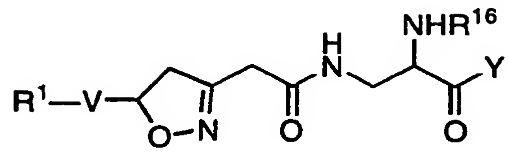
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
766	4-amidinophenyl	3-phenylpropyl-sulfonyl	OMe	
767	4-amidinophenyl	3-pyridylsulfonyl	OMe	
768	4-amidinophenyl	2-pyridylsulfonyl	OMe	

769	4-amidinophenyl	n-butylaminosulfonyl	OMe	
770	4-amidinophenyl	i-butylaminosulfonyl	OMe	
771	4-amidinophenyl	t-butylaminosulfonyl	OMe	
772	4-amidinophenyl	i-propylamino-sulfonyl	OMe	
773	4-amidinophenyl	cyclohexylamino-sulfonyl	OMe	
774	4-amidinophenyl	phenylaminosulfonyl	OMe	
775	4-amidinophenyl	benzylaminosulfonyl	OMe	
776	4-amidinophenyl	dimethylamino-sulfonyl	OMe	
777	2-fluoro-4-amidino-phenyl	3-methylphenyl-sulfonyl	OMe	
778	5-amidino-2-pyridyl	n-butyloxycarbonyl	OMe	
779	5-amidino-2-pyridyl	3-methylphenyl-sulfonyl	OMe	
780	6-amidino-3-pyridyl	n-butyloxycarbonyl	OMe	
781	6-amidino-3-pyridyl	3-methylphenyl-sulfonyl	OMe	
782	4-amidinophenyl	phenylaminocarbonyl	OMe	
783	4-amidinophenyl	benzylaminocarbonyl	OMe	
784	4-amidinophenyl	n-butylaminocarbonyl	OMe	
785	4-amidinophenyl	n-hexyloxycarbonyl	OMe	
786	4-amidinophenyl	n-hexyloxycarbonyl	OH	
787	4-amidinophenyl	isobutyloxycarbonyl	OMe	
788	4-amidinophenyl	isobutyloxycarbonyl	OH	
789	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OMe	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
790	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OH	
791	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OMe	
792	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OH	

793	4-amidinophenyl	n-propylsulfonyl	OMe	
794	4-amidinophenyl	2-methylphenyl-sulfonyl	OMe	
795	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	
796	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	
797	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OH	
798	4-amidinophenyl	3-methylphenylsulfonyl	OH	486

Table 2E



Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
801	4-amidinophenyl	benzyloxycarbonyl	OH	
802	4-amidinophenyl	t-butyloxycarbonyl	OH	
803	4-amidinophenyl	n-butyloxycarbonyl	OH	
804	4-amidinophenyl	ethyloxycarbonyl	OH	
805	4-amidinophenyl	methyloxycarbonyl	OH	
806	4-amidinophenyl	phenylethylcarbonyl	OH	
807	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OH	
808	4-amidinophenyl	n-pentylcarbonyl	OH	
809	4-amidinophenyl	n-butylcarbonyl	OH	
810	4-amidinophenyl	propionyl	OH	
811	4-amidinophenyl	acetyl	OH	
812	4-amidinophenyl	methylsulfonyl	OH	
813	4-amidinophenyl	ethylsulfonyl	OH	
814	4-amidinophenyl	n-butylsulfonyl	OH	
815	4-amidinophenyl	phenylsulfonyl	OH	
816	4-amidinophenyl	4-methylphenyl-sulfonyl	OH	488
817	4-amidinophenyl	benzylsulfonyl	OH	
818	4-amidinophenyl	2-pyridylcarbonyl	OH	
819	4-amidinophenyl	3-pyridylcarbonyl	OH	
820	4-amidinophenyl	4-pyridylcarbonyl	OH	
821	4-amidinophenyl	2-pyridylmethyl-carbonyl	OH	
822	4-amidinophenyl	3-pyridylmethyl-carbonyl	OH	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
823	4-amidinophenyl	4-pyridylmethyl-carbonyl	OH	
824	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OH	
825	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OH	
826	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OH	
827	4-amidinophenyl	benzyloxycarbonyl	OMe	
828	4-amidinophenyl	t-butyloxycarbonyl	OMe	
829	4-amidinophenyl	n-butyloxycarbonyl	OMe	448
830	4-amidinophenyl	ethyloxycarbonyl	OMe	
831	4-amidinophenyl	methyloxycarbonyl	OMe	
832	4-amidinophenyl	phenylethylcarbonyl	OMe	
833	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OMe	
834	4-amidinophenyl	n-pentylcarbonyl	OMe	
835	4-amidinophenyl	n-butylcarbonyl	OMe	
836	4-amidinophenyl	propionyl	OMe	
837	4-amidinophenyl	acetyl	OMe	
838	4-amidinophenyl	methylsulfonyl	OMe	
839	4-amidinophenyl	ethylsulfonyl	OMe	
840	4-amidinophenyl	n-butylsulfonyl	OMe	
841	4-amidinophenyl	phenylsulfonyl	OMe	
842	4-amidinophenyl	4-methylphenyl-sulfonyl	OMe	
843	4-amidinophenyl	benzylsulfonyl	OMe	
844	4-amidinophenyl	2-pyridylcarbonyl	OMe	
845	4-amidinophenyl	3-pyridylcarbonyl	OMe	
846	4-amidinophenyl	4-pyridylcarbonyl	OMe	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$

847	4-amidinophenyl	2-pyridylmethyl-carbonyl	OMe	
848	4-amidinophenyl	3-pyridylmethyl-carbonyl	OMe	
849	4-amidinophenyl	4-pyridylmethyl-carbonyl	OMe	
850	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OMe	
851	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OMe	
852	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OMe	
853	4-piperidinylethyl	benzylcarbonyl	OMe	
854	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	
855	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	
856	4-amidinophenyl	1-naphthylsulfonyl	OMe	
857	4-amidinophenyl	2-naphthylsulfonyl	OMe	
858	4-piperidinylethyl	n-butyloxycarbonyl	OMe	
859	4-amidinophenyl	2-thienylsulfonyl	OMe	
860	4-amidinophenyl	3-methylphenyl-sulfonyl	OMe	
861	4-amidinophenyl	4-fluorophenyl-sulfonyl	OMe	
862	4-amidinophenyl	4-methoxyphenyl-sulfonyl	OMe	
863	4-amidinophenyl	n-propylsulfonyl	OMe	
864	4-amidinophenyl	2-phenylethyl-sulfonyl	OMe	
865	4-amidinophenyl	4-isopropylphenyl-sulfonyl	OMe	

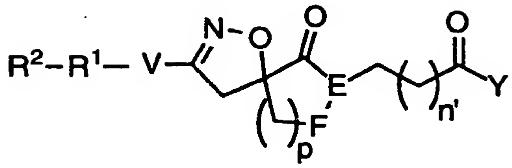
Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
866	4-amidinophenyl	3-phenylpropyl-sulfonyl	OMe	
867	4-amidinophenyl	3-pyridylsulfonyl	OMe	
868	4-amidinophenyl	2-pyridylsulfonyl	OMe	

869	4-amidinophenyl	n-butylaminosulfonyl	OMe	
870	4-amidinophenyl	i-butylaminosulfonyl	OMe	
871	4-amidinophenyl	t-butylaminosulfonyl	OMe	
872	4-amidinophenyl	i-propylamino-sulfonyl	OMe	
873	4-amidinophenyl	cyclohexylamino-sulfonyl	OMe	
874	4-amidinophenyl	phenylaminosulfonyl	OMe	
875	4-amidinophenyl	benzylaminosulfonyl	OMe	
876	4-amidinophenyl	dimethylamino-sulfonyl	OMe	
877	2-fluoro-4-amidino-phenyl	3-methylphenyl-sulfonyl	OMe	
878	5-amidino-2-pyridyl	n-butyloxycarbonyl	OMe	
879	5-amidino-2-pyridyl	3-methylphenyl-sulfonyl	OMe	
880	6-amidino-3-pyridyl	n-butyloxycarbonyl	OMe	
881	6-amidino-3-pyridyl	3-methylphenyl-sulfonyl	OMe	
882	4-amidinophenyl	phenylaminocarbonyl	OMe	
883	4-amidinophenyl	benzylaminocarbonyl	OMe	
884	4-amidinophenyl	n-butylaminocarbonyl	OMe	
885	4-amidinophenyl	n-hexyloxycarbonyl	OMe	
886	4-amidinophenyl	n-hexyloxycarbonyl	OH	
887	4-amidinophenyl	isobutyloxycarbonyl	OMe	
888	4-amidinophenyl	isobutyloxycarbonyl	OH	
889	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OMe	

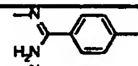
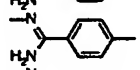
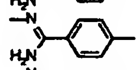
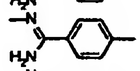
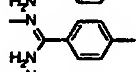
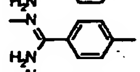
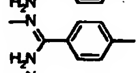
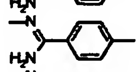
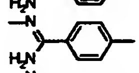
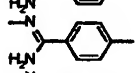
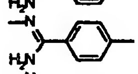
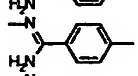
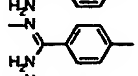
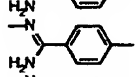
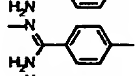
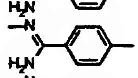
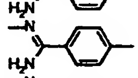
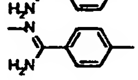
Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
890	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OH	
891	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OMe	
892	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OH	

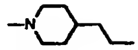
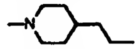
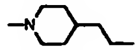
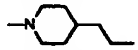
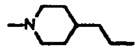
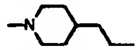
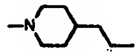
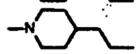
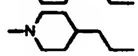
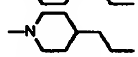
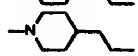
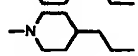
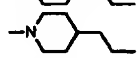
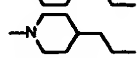
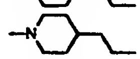
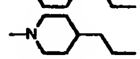
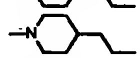
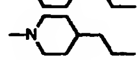
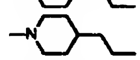
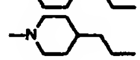
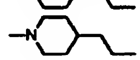
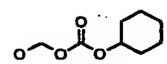
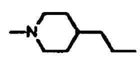
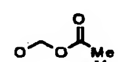
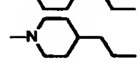
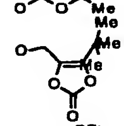
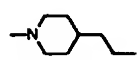
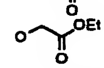
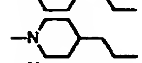
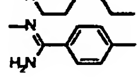
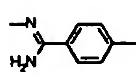
893	4-amidinophenyl	n-propylsulfonyl	OMe
894	4-amidinophenyl	2-methylphenyl-sulfonyl	OMe
895	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe
896	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe
897	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OH

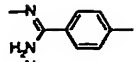
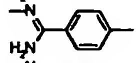
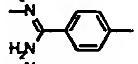
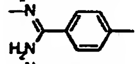
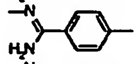
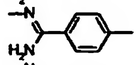
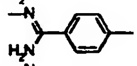
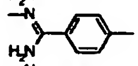
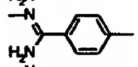
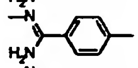
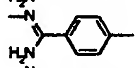
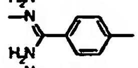
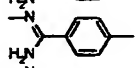
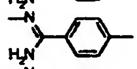
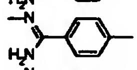
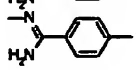
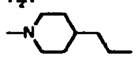
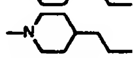
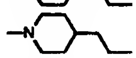
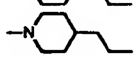
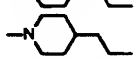
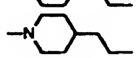
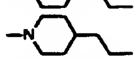
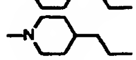
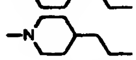
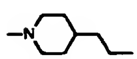
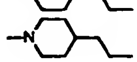
Table 3



(VII)

Ex. No.	R^2	R^1-V	-F-E<	p	n'	Y	MS $(M+H)^+$
171	H		-C(=O)-N<	1	1	OH	
172	H		-C(=O)-N<	1	2	OH	
173	H		$-C(H_2)-N<$	1	1	OH	
174	H		$-C(H_2)-N<$	1	2	OH	
175	H		-C(H)=C<	1	1	OH	
176	H		-C(H)=C<	1	2	OH	
177	H		-C(=O)-N<	2	1	OH	
178	H		-C(=O)-N<	2	2	OH	
179	H		$-C(H_2)-N<$	2	1	OH	
180	H		$-C(H_2)-N<$	2	2	OH	
181	H		-C(H)=C<	2	1	OH	
182	H		-C(H)=C<	2	2	OH	
183	H		-C(=O)-N<	3	1	OH	
184	H		-C(=O)-N<	3	2	OH	
185	H		$-C(H_2)-N<$	3	1	OH	
186	H		$-C(H_2)-N<$	3	2	OH	
187	H		-C(H)=C<	3	1	OH	
188	H		-C(H)=C<	3	2	OH	
Ex. No.	R^2	R^1-V	-F-E<	p	n'	Y	

189	H		-C(=O)-N<	1	1	OH	338
190	H		-C(=O)-N<	1	2	OH	352
191	H		-C(H_2)-N<	1	1	OH	
192	H		-C(H_2)-N<	1	2	OH	
193	H		-C(H)=C<	1	1	OH	
194	H		-C(H)=C<	1	2	OH	
195	H		-C(=O)-N<	2	1	OH	
196	H		-C(=O)-N<	2	2	OH	
197	H		-C(H_2)-N<	2	1	OH	
198	H		-C(H_2)-N<	2	2	OH	
199	H		-C(H)=C<	2	1	OH	
200	H		-C(H)=C<	2	2	OH	
201	H		-C(=O)-N<	3	1	OH	
202	H		-C(=O)-N<	3	2	OH	
203	H		-C(H_2)-N<	3	1	OH	
204	H		-C(H_2)-N<	3	2	OH	
205	H		-C(H)=C<	3	1	OH	
206	H		-C(H)=C<	3	2	OH	
207	Boc		-C(=O)-N<	1	1	OH	
208	Cbz		-C(=O)-N<	1	1	OH	
209	H		-C(=O)-N<	1	1		
210	H		-C(=O)-N<	1	1		
211	H		-C(=O)-N<	1	1		
212	H		-C(=O)-N<	1	1		
213	H		-C(=O)-N<	1	1		
214	H		-C(=O)-N<	1	1	OEt	
Ex. No.	R^2	R^1-V	-F-E<	p	n'	Y	
215	H		-C(=O)-N<	1	2	OEt	

216	H		-C(H2)-N<	1	1	OEt
217	H		-C(H2)-N<	1	2	OEt
218	H		-C(H)=C<	1	1	OEt
219	H		-C(H)=C<	1	2	OEt
220	H		-C(=O)-N<	2	1	OEt
221	H		-C(=O)-N<	2	2	OEt
222	H		-C(H2)-N<	2	1	OEt
223	H		-C(H2)-N<	2	2	OEt
224	H		-C(H)=C<	2	1	OEt
225	H		-C(H)=C<	2	2	OEt
226	H		-C(=O)-N<	3	1	OEt
227	H		-C(=O)-N<	3	2	OEt
228	H		-C(H2)-N<	3	1	OEt
229	H		-C(H2)-N<	3	2	OEt
230	H		-C(H)=C<	3	1	OEt
231	H		-C(H)=C<	3	2	OEt
232	H		-C(=O)-N<	1	1	OEt
233	H		-C(=O)-N<	1	2	OEt
234	H		-C(H2)-N<	1	1	OEt
235	H		-C(H2)-N<	1	2	OEt
236	H		-C(H)=C<	1	1	OEt
237	H		-C(H)=C<	1	2	OEt
238	H		-C(=O)-N<	2	1	OEt
239	H		-C(=O)-N<	2	2	OEt
240	H		-C(H2)-N<	2	1	OEt
Ex. No.	R^2	R^1-V	-F-E<	p	n'	Y
241	H		-C(H2)-N<	2	2	OEt
242	H		-C(H)=C<	2	1	OEt

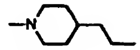
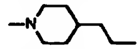
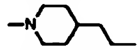
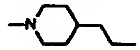
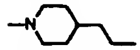
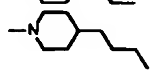
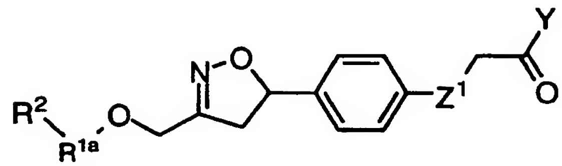
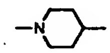
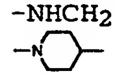
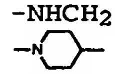
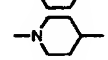
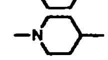
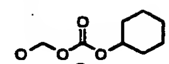
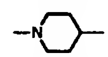
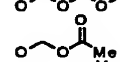
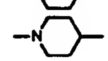
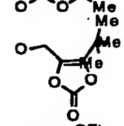
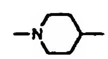
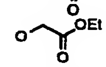
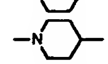
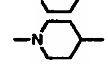
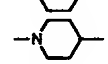
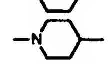
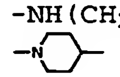
243	H		-C(H)=C<	2	2	OEt	
244	H		-C(=O)-N<	3	1	OEt	
245	H		-C(=O)-N<	3	2	OEt	
246	H		-C(H_2)-N<	3	1	OEt	
247	H		-C(H_2)-N<	3	2	OEt	
248	H		-C(H)=C<	3	1	OEt	
249	H		-C(H)=C<	3	2	OEt	
250	Boc		-C(=O)-N<	1	1	OEt	
251	Cbz		-C(=O)-N<	1	1	OEt	
373	H		-C(=O)-N<	1	2	OH	366

Table 4



(VIII)

Example Number	R^2	R^{1a}	Z^1	Y
252	H		CH_2	OH
253	H	$-NHCH_2)_2-$	CH_2	OH
254	H	$-NHCH_2)_3-$	CH_2	OH
255	H		O	OH
256	H	$-NHCH_2)_2-$	O	OH
257	H	$-NHCH_2)_3-$	O	OH
258	Boc		CH_2	OH
259	Cbz		CH_2	OH
260	H		CH_2	
261	H		CH_2	
262	H		CH_2	
263	H		CH_2	
264	H		CH_2	
265	H		CH_2	OEt
266	H		CH_2	OEt
267	H		CH_2	OEt
268	H	$-NH(CH_2)_2-$	CH_2	OEt
269	H	$-NH(CH_2)_3-$	CH_2	OEt
270	H		O	OEt
271	H	$-NH(CH_2)_2-$	O	OEt
272	H	$-NH(CH_2)_3-$	O	OEt

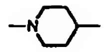
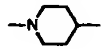
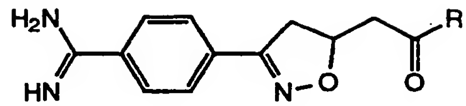
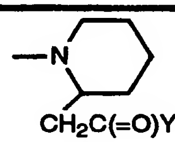
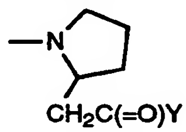
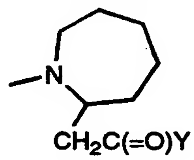
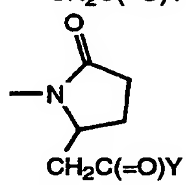
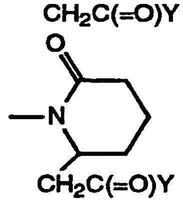
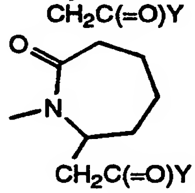
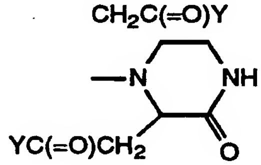
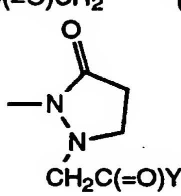
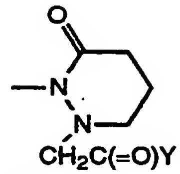
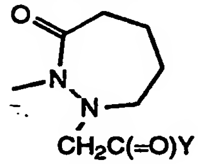
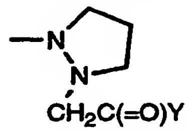
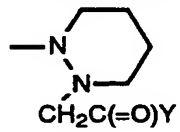
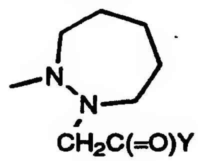
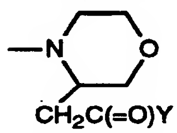
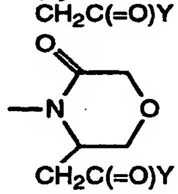
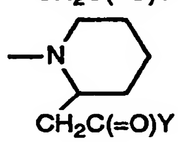
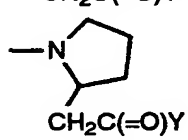
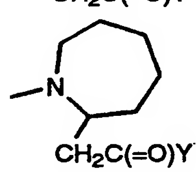
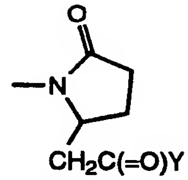
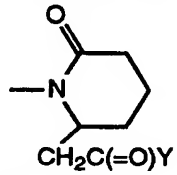
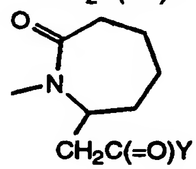
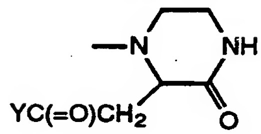
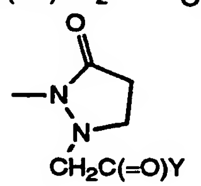
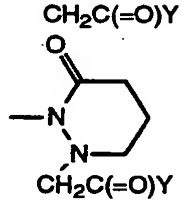
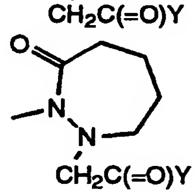
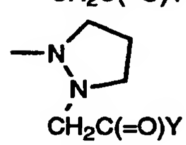
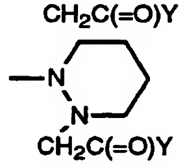
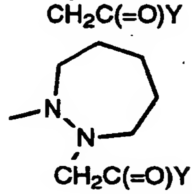
Example Number	R^2	R^{1a}	Z^1	Y
273	Boc		CH_2	OEt
274	Cbz		CH_2	OEt

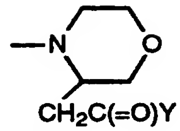
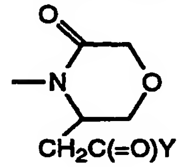
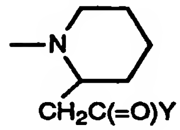
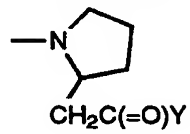
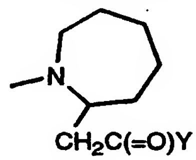
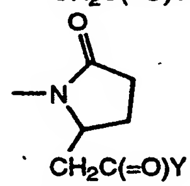
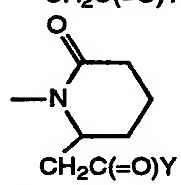
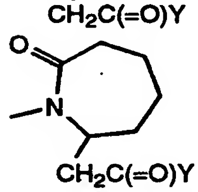
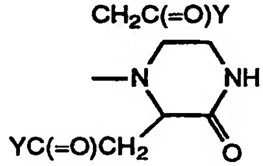
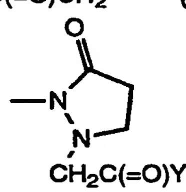
Table 5

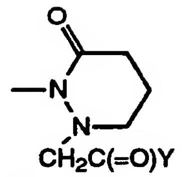
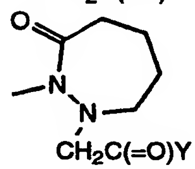
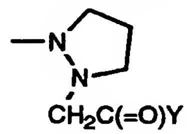
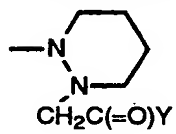
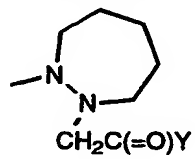
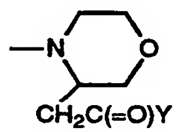
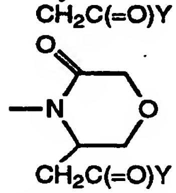
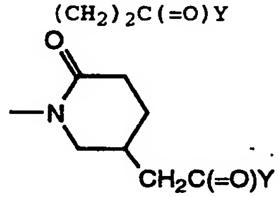
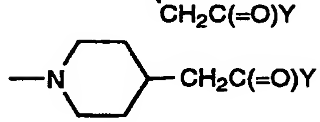
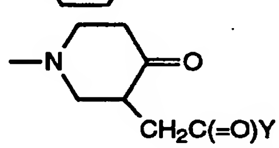


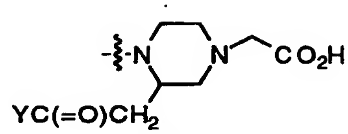
Example Number	R	Y	MS(ESI) (M+H)+
375		OH	373
376		OH	
377		OH	387
378		OH	
379		OH	
380		OH	
381		OH	
382		OH	

383		OH	415
384		OH	
385		OH	
386		OH	
387		OH	
388		OH	
389		OH	
394		OMe	387
395		OMe	
396		OMe	

397		OMe	
398		OMe	
399		OMe	
400		OMe	402
401		OMe	
402		OMe	
403		OMe	
404		OMe	
405		OMe	
406		OMe	

407		OMe	
408		OMe	
413		OEt	401
414		OEt	
415		OEt	415
416		OEt	
417		OEt	
418		OEt	
419		OEt	
420		OEt	

421		OEt	
422		OEt	
423		OEt	
424		OEt	
425		OEt	
426		OEt	
427		OEt	
432	$-NHC(CH_3)_2-$ $CH_2C(=O)Y$	OEt.	
433	$-N(CH_2C_6H_5)-$ $(CH_2)_2C(=O)Y$	OEt	
436		OEt	387
437		OEt	387
438		OMe	387

899  OMe

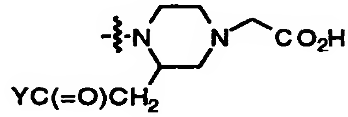
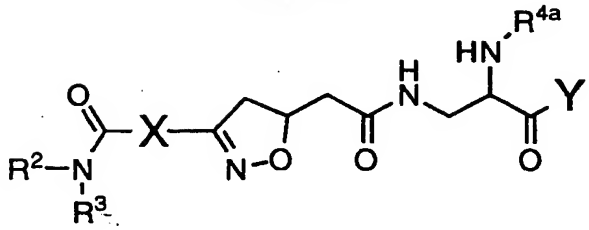
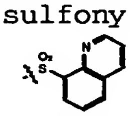
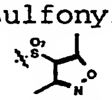
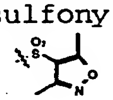
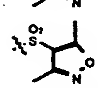
900  OH

Table 6



Ex. No.	R^2	R^3	R^{4a}	X	Y	(M+H) + ESI
950	H	H	3-methyl-phenyl-sulfonyl	2-fluoro-phen-1,4-diyl	OCH_3	521
951	H	H	3-methyl-phenyl-sulfonyl	2-fluoro-phen-1,4-diyl	OH	507
952		H	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OCH_3	545
953		H	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	532
954	H	H	n-butoxy-carbonyl	-phen-1,4-diyl	OH	435
955	H	H	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OCH_3	503
956	H	H	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	489
957	H	H		-phen-1,4-diyl	OH	527
958	H	H	4-CF_3-phenyl-sulfonyl	-phen-1,4-diyl	OH	543
959	H	H		-phen-1,4-diyl	OH	
960	o-CH_3O-benzyl	H	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	
961	o-CH_3O-benzyl	H		-phen-1,4-diyl	OH	
962	o-CH_3O-benzyl	CH_3		-phen-1,4-diyl	OH	
963	o-CH_3O-benzyl	CH_3	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	

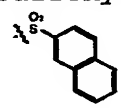
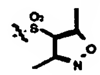
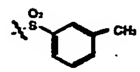
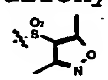
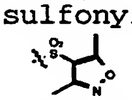
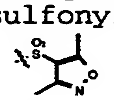
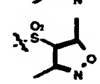
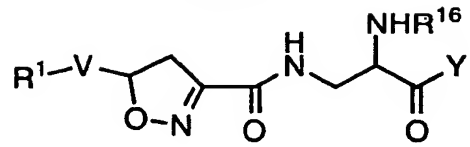
964	H	H	2-fluoro-phenyl-sulfonyl	-phen-1,4-diyl	OH	493
965	H	H	4-CF_3-phenyl-sulfonyl	-phen-1,4-diyl	OH	543
966	H	H	4-Cl-phenyl-sulfonyl	-phen-1,4-diyl	OH	509
967	H	H		-phen-1,4-diyl	OH	525
968	3-(CF_3)-benzyl	H		-phen-1,4-diyl	OH	
969	3-(CF_3)-benzyl	H		-phen-1,4-diyl	OH	
970	3-(CF_3)-benzyl	CH3	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	
971	3-(CF_3)-benzyl	CH3		-phen-1,4-diyl	OH	
972	nBu-	H	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	
973	nBu-	H		-phen-1,4-diyl	OH	
974	nBu-	CH3	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	
975	nBu-	CH3		-phen-1,4-diyl	OH	
976	CH3	CH3		-phen-1,4-diyl	OH	
977	CH3	CH3	3-methyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	
978	H	H	3-methyl-phenyl-sulfonyl	5-carboxamido pyrid-2-yl	OMe	490
979	H	H	4-ethyl-phenyl-sulfonyl	-phen-1,4-diyl	OH	503

Table 7



Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$
980	4-amidinophenyl	H	OH	
981	4-amidinophenyl	benzyloxycarbonyl	OH	
982	4-amidinophenyl	t-butyloxycarbonyl	OH	
983	4-amidinophenyl	n-butyloxycarbonyl	OH	
984	4-amidinophenyl	ethyloxycarbonyl	OH	
985	4-amidinophenyl	methyloxycarbonyl	OH	
986	4-amidinophenyl	phenylethylcarbonyl	OH	
987	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OH	
988	4-amidinophenyl	n-pentylcarbonyl	OH	
989	4-amidinophenyl	n-butylcarbonyl	OH	
990	4-amidinophenyl	propionyl	OH	
991	4-amidinophenyl	acetyl	OH	
992	4-amidinophenyl	methylsulfonyl	OH	
993	4-amidinophenyl	ethylsulfonyl	OH	
994	4-amidinophenyl	n-butylsulfonyl	OH	
995	4-amidinophenyl	phenylsulfonyl	OH	
996	4-amidinophenyl	4-methylphenyl-sulfonyl	OH	474
997	4-amidinophenyl	benzylsulfonyl	OH	
998	4-amidinophenyl	2-pyridylcarbonyl	OH	
999	4-amidinophenyl	3-pyridylcarbonyl	OH	
1000	4-amidinophenyl	4-pyridylcarbonyl	OH	
1001	4-amidinophenyl	2-pyridylmethyl-carbonyl	OH	
1002	4-amidinophenyl	3-pyridylmethyl-carbonyl	OH	
Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$

1003	4-amidinophenyl	4-pyridylmethyl-carbonyl	OH	
1004	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OH	
1005	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OH	
1006	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OH	
1007	4-amidinophenyl	H	OMe	
1008	4-amidinophenyl	benzyloxycarbonyl	OMe	
1009	4-amidinophenyl	t-butyloxycarbonyl	OMe	
1010	4-amidinophenyl	n-butyloxycarbonyl	OMe	
1011	4-amidinophenyl	ethyloxycarbonyl	OMe	
1012	4-amidinophenyl	methyloxycarbonyl	OMe	
1013	4-amidinophenyl	phenylethylcarbonyl	OMe	
1014	4-amidinophenyl	2,2-dimethyl-propylcarbonyl	OMe	
1015	4-amidinophenyl	n-pentylcarbonyl	OMe	
1016	4-amidinophenyl	n-butylcarbonyl	OMe	
1017	4-amidinophenyl	propionyl	OMe	
1018	4-amidinophenyl	acetyl	OMe	
1019	4-amidinophenyl	methylsulfonyl	OMe	
1020	4-amidinophenyl	ethylsulfonyl	OMe	
1021	4-amidinophenyl	n-butylsulfonyl	OMe	
1022	4-amidinophenyl	phenylsulfonyl	OMe	
1023	4-amidinophenyl	4-methylphenyl-sulfonyl	OMe	
1024	4-amidinophenyl	benzylsulfonyl	OMe	
1025	4-amidinophenyl	2-pyridylcarbonyl	OMe	
1026	4-amidinophenyl	3-pyridylcarbonyl	OMe	
1027	4-amidinophenyl	4-pyridylcarbonyl	OMe	
Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$
1029	4-amidinophenyl	2-pyridylmethyl-carbonyl	OMe	
1030	4-amidinophenyl	3-pyridylmethyl-carbonyl	OMe	

1031	4-amidinophenyl	4-pyridylmethyl-carbonyl	OMe	
1032	4-amidinophenyl	2-pyridylmethoxy-carbonyl	OMe	
1033	4-amidinophenyl	3-pyridylmethoxy-carbonyl	OMe	
1034	4-amidinophenyl	4-pyridylmethoxy-carbonyl	OMe	
1035	4-piperidinylethyl	benzylcarbonyl	OMe	
1036	4-(BOCamidino)phenyl	benzyloxycarbonyl	OMe	
1037	4-(BOCamidino)phenyl	n-butyloxycarbonyl	OMe	
1038	4-amidinophenyl	1-naphthylsulfonyl	OMe	
1039	4-amidinophenyl	2-naphthylsulfonyl	OMe	
1040	4-amidinophenyl	styrylsulfonyl	OMe	
1041	4-piperidinylethyl	n-butyloxycarbonyl	OMe	
1042	4-amidinophenyl	4-butyloxyphenyl-sulfonyl	OMe	
1043	4-amidinophenyl	2-thienylsulfonyl	OMe	
1044	4-amidinophenyl	3-methylphenyl-sulfonyl	OMe	
1045	4-amidinophenyl	4-iodophenyl	OMe	
1046	4-amidinophenyl	3-trifluoromethyl-phenylsulfonyl	OMe	
1047	4-amidinophenyl	3-chlorophenyl-sulfonyl	OMe	
1048	4-amidinophenyl	2-methoxycarbonyl-phenylsulfonyl	OMe	
Ex No.	R^1–V	R^{16}	Y	MS $(M+H)^+$
1050	4-amidinophenyl	2,4,6-trimethyl-phenylsulfonyl	OMe	
1051	4-amidinophenyl	2-chlorophenyl-sulfonyl	OMe	
1052	4-amidinophenyl	2-trifluoromethyl-phenylsulfonyl	OMe	
1053	4-amidinophenyl	4-trifluoromethyl-phenylsulfonyl	OMe	

1054	4-amidinophenyl	2-fluorophenyl-sulfonyl	OMe	
1055	4-amidinophenyl	4-fluorophenyl-sulfonyl	OMe	
1056	4-amidinophenyl	4-methoxyphenyl-sulfonyl	OMe	
1057	4-amidinophenyl	2,3,5,6-tetramethyl-phenylsulfonyl	OMe	
1058	4-amidinophenyl	4-cyanophenyl-sulfonyl	OMe	
1059	4-amidinophenyl	4-chlorophenyl-sulfonyl	OMe	
1060	4-amidinophenyl	4-ethylphenyl-sulfonyl	OMe	
1061	4-amidinophenyl	4-propylphenyl-sulfonyl	OMe	
1062	4-amidinophenyl	n-propylsulfonyl	OMe	
1063	4-amidinophenyl	2-phenylethyl-sulfonyl	OMe	
1064	4-amidinophenyl	4-isopropylphenyl-sulfonyl	OMe	
1065	4-amidinophenyl	3-phenylpropyl-sulfonyl	OMe	
1066	4-amidinophenyl	3-pyridylsulfonyl	OMe	
Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$
1068	4-amidinophenyl	2-pyridylsulfonyl	OMe	
1069	4-amidinophenyl	2,2-diphenyl-1-ethenylsulfonyl	OMe	
1070	4-amidinophenyl	2-pyrimidinyl-sulfonyl	OMe	
1071	4-amidinophenyl	4-methyl-2-pyrimidinylsulfonyl	OMe	
1072	4-amidinophenyl	4,6-dimethyl-2-pyrimidinylsulfonyl	OMe	
1073	4-amidinophenyl	1,2,4-triazol-3-ylsulfonyl	OMe	

1074	4-amidinophenyl	1-methyl-1,3,4-triazol-5-ylsulfonyl	OMe	
1075	4-amidinophenyl	3,5-dimethyl-4-pyrazolylsulfonyl	OMe	
1076	4-amidinophenyl	1-phenyl-4-pyrazolylsulfonyl	OMe	
1077	4-amidinophenyl	n-butylaminosulfonyl	OMe	
1078	4-amidinophenyl	i-butylaminosulfonyl	OMe	
1079	4-amidinophenyl	t-butylaminosulfonyl	OMe	
1080	4-amidinophenyl	i-propylamino-sulfonyl	OMe	
1081	4-amidinophenyl	cyclohexylamino-sulfonyl	OMe	
1082	4-amidinophenyl	phenylaminosulfonyl	OMe	
1083	4-amidinophenyl	benzylaminosulfonyl	OMe	
1084	4-amidinophenyl	dimethylamino-sulfonyl	OMe	
1085	4-amidino-2-fluoro-phenyl	3-methylphenyl-sulfonyl	OMe	
1086	2-amidino-5-pyridyl	n-butyloxycarbonyl	OMe	
Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$
1088	2-amidino-5-pyridyl	3-methylphenyl-sulfonyl	OMe	
1089	3-amidino-6-pyridyl	n-butyloxycarbonyl	OMe	
1090	3-amidino-6-pyridyl	3-methylphenyl-sulfonyl	OMe	
1091	4-amidinophenyl	phenylaminocarbonyl	OMe	
1092	4-amidinophenyl	4-fluorophenylamino-carbonyl	OMe	
1093	4-amidinophenyl	1-naphthylamino-carbonyl	OMe	
1094	4-amidinophenyl	benzylaminocarbonyl	OMe	
1095	4-amidinophenyl	n-butylaminocarbonyl	OMe	
1096	4-amidinophenyl	4-ethylphenyl-carbonyl	OMe	
1097	4-amidinophenyl	biphenylcarbonyl	OMe	

1098	4-amidinophenyl	2-naphthylcarbonyl	OMe	
1099	4-amidinophenyl	(2-chlorophenyl) methoxycarbonyl	OMe	
1100	4-amidinophenyl	(2-chlorophenyl) methoxycarbonyl	OH	
1101	4-amidinophenyl	(2-bromophenyl) methoxycarbonyl	OMe	
1102	4-amidinophenyl	(2-bromophenyl) methoxycarbonyl	OH	
1103	4-amidinophenyl	n-hexyloxycarbonyl	OMe	
1104	4-amidinophenyl	n-hexyloxycarbonyl	OH	
1105	4-amidinophenyl	isobutyloxycarbonyl	OMe	
1106	4-amidinophenyl	isobutyloxycarbonyl	OH	
1107	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OMe	
1108	4-amidinophenyl	2-cyclopropylethoxy-carbonyl	OH	

Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$
1110	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OMe	
1111	4-amidinophenyl	2-cyclopentylethoxy-carbonyl	OH	
1112	4-amidinophenyl	4,4,4-trifluoro-butyloxycarbonyl	OMe	
1113	4-amidinophenyl	4,4,4-trifluoro-butyloxycarbonyl	OH	
1114	4-amidinophenyl	n-propylsulfonyl	OH	
1115	4-amidinophenyl	2-methylphenyl-sulfonyl	OMe	
1116	4-amidinophenyl	4-chloro-2,5-dimethyl-phenylsulfonyl	OH	536
1117	4-amidinophenyl	2,3-dichlorophenyl-sulfonyl	OMe	
1118	4-amidinophenyl	2-bromophenyl-sulfonyl	OMe	

1119	4-amidinophenyl	3-bromophenyl-sulfonyl	OMe	
1120	4-amidinophenyl	4-bromophenyl-sulfonyl	OMe	
1121	4-amidinophenyl	biphenylsulfonyl	OMe	
1122	4-amidinophenyl	5-chloro-1,3-dimethyl-4-pyrazolyl	OMe	
1123	4-amidinophenyl	3-bromo-2-thienylsulfonyl	OMe	
1124	4-amidinophenyl	5-bromo-2-thienylsulfonyl	OMe	
1125	4-amidinophenyl	5-[1-methyl-5-trifluoromethyl-3-pyrazolyl]-2-thienylsulfonyl	OMe	

Ex No.	R^1–V	R^{16}	Y	MS $(M+H)^+$
1127	4-amidinophenyl	5-(3-isoxazolyl)-2-thienylsulfonyl	OMe	
1128	4-amidinophenyl	5-(2-pyridinyl)-2-thienylsulfonyl	OMe	
1129	4-amidinophenyl	4-methyl-2-methylcarbonylamino-5-thiazolylsulfonyl	OMe	
1130	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	
1131	4-amidinophenyl	2-benzothienyl-sulfonyl	OMe	
1132	4-amidinophenyl	3-methyl-2-benzothienylsulfonyl	OMe	
1133	4-amidinophenyl	8-quinolinylsulfonyl	OMe	
1134	4-amidinophenyl	8-quinolinylsulfonyl	OH	
1135	4-amidinophenyl	2,1,3-benzo-thiadiazol-4-ylsulfonyl	OMe	
1136	4-amidinophenyl	2,1,3-benzo-thiadiazol-4-ylsulfonyl	OH	

1137	4-amidinophenyl	4-N,N-dimethylamino-1-naphthylsulfonyl	OMe	
1138	4-amidinophenyl	4-N,N-dimethylamino-1-haphthylsulfonyl	OH	
1139	4-amidinophenyl	2,1,3-benzoxadiazol-4-ylsulfonyl	OMe	
1140	4-amidinophenyl	2,1,3-benzoxadiazol-4-ylsulfonyl	OH	
1141	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OMe	
Ex No.	R^1—V	R^{16}	Y	MS $(M+H)^+$
1143	4-amidinophenyl	2,2,5,7,8-pentamethyl 3,4-dihydro-2Hbenzo-pyran-6-ylsulfonyl	OH	
1144	4-N-methylamidino phenyl	3-methylphenylsulfonyl	OMe	
1145	4-N-ethylamidino phenyl	3-methylphenylsulfonyl	OMe	
1146	4-N-n-propylamidino phenyl	3-methylphenylsulfonyl	OMe	
1147	4-N-benzylamidino phenyl	3-methylphenylsulfonyl	OMe	
1148	4-N-n-butylamidino phenyl	3-methylphenylsulfonyl	OMe	
1149	4-N-methylamidino phenyl	3-methylphenylsulfonyl	OH	
1150	4-N-ethylamidino phenyl	3-methylphenylsulfonyl	OH	
1151	4-N-n-propylamidino phenyl	3-methylphenylsulfonyl	OH	
1152	4-N-benzylamidino phenyl	3-methylphenylsulfonyl	OH	
1153	4-N-n-butylamidino phenyl	3-methylphenylsulfonyl	OH	

1154	4-N-methylamidino-phenyl	n-butyloxycarbonyl	OMe	
1155	4-N-ethylamidinophenyl	n-butyloxycarbonyl	OMe	
1156	4-N-npropylamidino-phenyl	n-butyloxycarbonyl	OMe	
1157	4-N-n-butylamidino-phenyl	n-butyloxycarbonyl	OMe	
1158	4-N-benzylamidino-phenyl	n-butyloxycarbonyl	OMe	
Ex No.	R^1–V	R^{16}	Y	MS $(M+H)^+$
1160	4-N-methylamidino-phenyl	n-butyloxycarbonyl	OH	
1161	4-N-ethylamidino-phenyl	n-butyloxycarbonyl	OH	
1162	4-N-n-propylamidino-phenyl	n-butyloxycarbonyl	OH	
1163	4-N-n-butylamidino-phenyl	n-butyloxycarbonyl	OH	
1164	4-N-benzylamidino-phenyl	n-butyloxycarbonyl	OH	
1165	4-(acetoxyamidino)-phenyl	n-butyloxycarbonyl	OMe	
1166	4-(acetoxyamidino)-phenyl	n-butyloxycarbonyl	OH	
1167	4-(acetoxyamidino)-phenyl	isobutyloxycarbonyl	OMe	
1168	4-(acetoxyamidino)-phenyl	isobutyloxycarbonyl	OH	
1169	4-(acetoxyamidino)-phenyl	cyclopropylethoxy-carbonyl	OMe	
1170	4-(acetoxyamidino)-phenyl	cyclopropylethoxy-carbonyl	OH	
1171	4-(acetoxyamidino)-phenyl	benzyloxycarbonyl	OMe	
1172	4-(acetoxyamidino)-phenyl	benzyloxycarbonyl	OH	

1173	4-(acetoxyamidino)-phenyl	4-methylphenylsulfonyl	OMe
1174	4-(acetoxyamidino)-phenyl	4-methylphenylsulfonyl	OH
1175	4-piperidinylethyl	n-butyloxycarbonyl	OMe
1176	4-piperidinylethyl	benzyloxycarbonyl	OMe
1177	4-piperidinylethyl	n-propyloxycarbonyl	OMe
1178	4-piperidinylethyl	isobutyloxycarbonyl	OMe
1179	4-piperidinylethyl	2-methylphenylsulfonyl	OMe
1180	4-piperidinylethyl	3-methylphenylsulfonyl	OMe
1181	4-piperidinylethyl	4-methylphenylsulfonyl	OMe
1182	4-piperidinylethyl	2-bromophenylsulfonyl	OMe
1183	4-piperidinylethyl	3-bromophenylsulfonyl	OMe
1184	4-piperidinylethyl	2-methoxyphenylsulfonyl	OMe
1185	4-piperidinylethyl	3-methoxyphenylsulfonyl	OMe
1186	4-piperidinylethyl	3-trifluoromethylphenyl sulfonyl	OMe
1187	4-piperidinylethyl	n-propylsulfonyl	OMe
1188	4-piperidinylethyl	n-butylsulfonyl	OMe
1189	4-piperidinylethyl	isopropylsulfonyl	OMe
1190	4-piperidinylethyl	isobutylsulfonyl	OMe
1191	4-piperidinylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1192	4-piperidinylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1193	4-piperidinylpropyl	n-butyloxycarbonyl	OMe
1194	4-piperidinylpropyl	n-propyloxycarbonyl	OMe
1195	4-piperidinylpropyl	benzyloxycarbonyl	OMe
1196	4-piperidinylpropyl	isobutyloxycarbonyl	OMe
1197	4-piperidinylpropyl	2-methylphenyl-sulfonyl	OMe
1198	4-piperidinylpropyl	3-methylphenyl-sulfonyl	OMe
1199	4-piperidinylpropyl	4-methylphenyl-sulfonyl	OMe
1200	4-piperidinylpropyl	2-bromophenylsulfonyl	OMe
1201	4-piperidinylpropyl	n-butylsulfonyl	OMe
1202	4-piperidinylpropyl	isobutylsulfonyl	OMe
1203	4-piperidinylpropyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1204	4-piperidinylpropyl	2,4-dimethyl-thiazoylsulfonyl	OMe
1205	4-piperidinylethyl	n-butyloxycarbonyl	OH
1206	4-piperidinylethyl	n-propyloxycarbonyl	OH
1207	4-piperidinylethyl	benyloxycarbonyl	OH
1208	4-piperidinylethyl	isobutyloxycarbonyl	OH
1209	4-piperidinylethyl	2-methylphenyl-sulfonyl	OH
1210	4-piperidinylethyl	3-methylphenyl-sulfonyl	OH
1211	4-piperidinylethyl	4-methylphenyl-sulfonyl	OH
1212	4-piperidinylethyl	2-bromophenylsulfonyl	OH
1213	4-piperidinylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH

1214	4-piperidinylethyl	2,4-dimethyl-thiazolylsulfonyl	OH
1215	4-piperidinylethyl	n-butylsulfonyl	OH
1216	4-piperidinylethyl	isobutylsulfonyl	OH
1217	4-piperidinylpropyl	n-butyloxycarbonyl	OH
1218	4-piperidinylpropyl	n-propyloxycarbonyl	OH
1219	4-piperidinylpropyl	isobutyloxycarbonyl	OH
1220	4-piperidinylpropyl	2-methylphenyl-carbonyl	OH
1221	4-piperidinylpropyl	4-methylphenyl-carbonyl	OH
1222	4-piperidinylpropyl	2-bromophenyl-carbonyl	OH
1223	4-piperidinylpropyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1224	4-piperidinylpropyl	n-butylsulfonyl	OH
1225	4-piperidinylpropyl	isobutylsulfonyl	OH
1226	4-amidinopiperidinyl	n-butyloxycarbonyl	OMe
1227	4-amidinopiperidinyl	isobutyloxycarbonyl	OMe
1228	4-amidinopiperidinyl	n-propyloxycarbonyl	OMe
1229	4-amidinopiperidinyl	benzyloxycarbonyl	OMe
1230	4-amidinopiperidinyl	n-butylsulfonyl	OMe
1231	4-amidinopiperidinyl	isobutylsulfonyl	OMe
1232	4-amidinopiperidinyl	n-propylsulfonyl	OMe
1233	4-amidinopiperidinyl	2-methylphenyl-sulfonyl	OMe
1234	4-amidinopiperidinyl	4-methylphenyl-sulfonyl	OMe
1235	4-amidinopiperidinyl	benzylsulfonyl	OMe
1236	4-amidinopiperidinyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1237	4-amidinopiperidinyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1238	4-amidinopiperidinyl	4-methylphenyl-sulfonyl	OH
1239	4-amidinopiperidinyl	n-butyloxycarbonyl	OH
1240	4-amidinopiperidinyl	isobutyloxycarbonyl	OH
1241	4-amidinopiperidinyl	n-propyloxycarbonyl	OH
1242	4-amidinopiperidinyl	benzyloxycarbonyl	OH
1243	4-amidinopiperidinyl	n-butylsulfonyl	OH
1244	4-amidinopiperidinyl	isobutylsulfonyl	OH
1245	4-amidinopiperidinyl	2-methylphenyl-sulfonyl	OH
1246	4-amidinopiperidinyl	3-methylphenyl-sulfonyl	OH
1247	4-amidinopiperidinyl	4-methylphenyl-sulfonyl	OH
1248	4-amidinopiperidinyl	2-bromophenylsulfonyl	OH
1249	4-amidinopiperidinyl	3-bromophenylsulfonyl	OH
1250	4-amidinopiperidinyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1251	4-amidinopiperidinyl	2,4-dimethyl-thiazolylsulfonyl	OH
1252	4-amidino-piperidinylmethyl	n-butyloxycarbonyl	OMe
1253	4-amidino-piperidinylmethyl	n-propyloxycarbonyl	OMe
1254	4-amidino-piperidinylmethyl	benzyloxycarbonyl	OMe
1255	4-amidino-piperidinylmethyl	n-butylsulfonyl	OMe

mM Tris HCl, 100 mM NaCl, 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2 \cdot 6H_2O$, 1.0 mM $MnCl_2 \cdot 4H_2O$). Receptor is then blocked (200 µl/well) with 3.5% BSA in B/B buffer for 2 hours at room temperature. After washing once with 1.0% BSA in B/B buffer, biotinylated vitronectin (100 µl) and either inhibitor (11 µl) or B/B buffer w/1.0% BSA (11 µl) is added to each well. The plates are incubated 2 hours at room temperature. The plates are washed twice with B/B buffer and incubated 1 hour at room temperature with anti-biotin alkaline phosphatase (100 µl/well) in B/B buffer containing 1.0% BSA. The plates are washed twice with B/B buffer and alkaline phosphatase substrate (100 µl) is added. Color is developed at room temperature. Color development is stopped by addition of 2N NaOH (25 µl/well) and absorbance is read at 405 nm. The IC_{50} is the concentration of test substance needed to block 50% of the vitronectin binding to the receptor.

Integrin Cell-Based Adhesion Assays

In the adhesion assays, a 96 well plate was coated with the ligand (i.e., fibrinogen) and incubated overnight at 4° C. The following day, the cells were harvested, washed and loaded with a fluorescent dye. Compounds and cells were added together and then were immediately added to the coated plate. After incubation, loose cells are removed from the plate, and the plate (with adherent cells) is counted on a fluorometer. The ability of test compounds to inhibit cell adhesion by 50% is given by the IC_{50} value and represents a measure of potency of inhibition of integrin mediated binding. Compounds were tested for their ability to block cell adhesion using assays specific for α_v/β_3, α_v/β_5 and α_5/β_1 integrin interactions.

Dosage and Formulation

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or

measure the binding of a specific integrin to a native ligand, for example, using the ELISA assay described below for the binding of vitronectin to the α_v/β_3 receptor. The compounds provided by this invention are also useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit integrin-ligand binding. These would be provided in commercial kits comprising a compound of this invention.

<u>Purified α_v/β_3 (human placenta) - Vitronectin ELISA:</u>

The α_v/β_3 receptor was isolated from human placental extracts prepared using octylglucoside. The extracts were passed over an affinity column composed of anti-α_v/β_3 monoclonal antibody (LM609) to Affigel. The column was subsequently washed extensively at pH 7 and pH 4.5 followed by elution at pH 3. The resulting sample was concentrated by wheat germ agglutinin chromatography to provide gave two bands on SDS gel which were confirmed as α_v/β_3 by western blotting.

Affinity purified protein was diluted at different levels and plated to 96 well plates. ELISA was performed using fixed concentration of biotinylated vitronectin (approximately 80 nM/well). This receptor preparation contains the α_v/β_3 with no detectable levels of α_v/β_5 according to the gel (α_v/β_3) and according to effects of blocking antibodies for the α_v/β_3 or α_v/β_5 in the ELISA.

A submaximal concentration of biotinylated vitronectin was selected based on conc. response curve with fixed receptor conc. and variable concentrations of biotinylated vitronectin.

<u>α_v/β_3-Vitronectin Binding Assay</u>

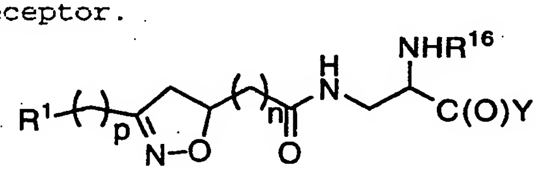
The purified receptor is diluted with coating buffer (20 mM Tris HCl, 150 mM NaCl, 2.0 mM $CaCl_2$, 1.0 mM $MgCl_2 \cdot 6H_2O$, 1.0 mM $MnCl_2 \cdot 4H_2O$) and coated (100 µl/well) on Costar (3590) high capacity binding plates overnight at 4°C. The coating solution is discarded and the plates washed once with blocking/binding buffer (B/B buffer, 50

2120	+++
2280	+++
2281	+++
2400	+++
2401	+++
2402	+++
2403	+++
2404	+++
2405	+++
2406	+++

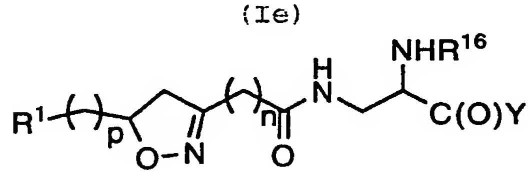
* Single diastereomer, racemic
† S isomer at C5 of isoxazoline ring
†† R isomer at C5 of isoxazoline ring

The compounds of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, inflammation, bone degradation, thrombosis, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoarthritis, atherosclerosis, metastasis, wound healing, diabetic retinopathy, inflammatory bowel disease and other angiogenic disorders.

The compounds of the formulae (Ie) and (If) possess selectivity as antagonists of integrins such as the α_v/β_3 vitronectin receptor.



(Ie)



(If)

The integrin antagonist activity of the compounds of the present invention is demonstrated using assays which

552		+++
553		+++
554		+++
555		+++
556		+++
587A (2S)††	+++	
588		+++
602		+++
611		+++
612		+++
613		+++
616	+++	
642		+++
643		+++
644		+++
651		+++
727		+++
729		+++
798		+++
829		+++
1284		+++
1321		+++
1525		+++
1694		+++
1731		+++
2104		+++
2109		+++
2110		+++
2111		+++
2112		+++
2113		+++
2114		+++
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2116		+++
2117		+++
2118		+++
2119		+++

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549		+++
550		+++
551		+++

472	+++
473	+++
473A (2S) †	+++
473B (2S) ††	+++
474	+++
475	+++
476	+++
477	+++
478	+++
479	+++
480	+++
481	+++
482	+++
483	+++
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415		+++
435		+++
436		+++
437		+++
438		+++
439		+++
440		+++
441	+++	
442		+++
443 (2S)		+++
444 (2S)		+++
445 (2S)		+++
446		+++
449A		+++
449B		+++
450		+++
451		+++
452		+++
453		+++
454		+++
455		+++
456		++
457		+++
458A	+++	
458B	+++	
460A	+++	
460B	+++	
462		+++
463	+++	
464		+++
465		+++
466		+++
467		+++
468		+++
469		+++
470		+++
471		+++

275		+++
276		+++
278		+++
290		+++
300		+++
312		+++
314A (2S)†		+++
314B (2S)††		+++
323		+++
324		+++
326		+++
327 (2S)		+++
328 (2S)		+++
338 (3S)	+	+++
339 (3S)	+++	
340 (3S)	+	++
341 (3S)	+++	
342 (2S)	+++	
344 (3R)		+++
345		+++
347 (3R)††		+++
348 (3R)		+++
350		+++
359		+++
362		+++
365		+++
368		+++
373	++	
371A		+++
371B		+++
374 (2S)	+	+++
375*	+++	
377	+++	
394		+++
394A††		+++
400	+++	
413*		+++

retinopathy, inflammatory bowel disease and other autoimmune diseases.

Table A below sets forth the antiplatelet activity of representative compounds of the present invention. The indicated compounds were tested for their ability to inhibit platelet aggregation (using platelet rich plasma (PRP)). The IC_{50} value (the concentration of antagonist which inhibits platelet aggregation by 50% relative to a control lacking the antagonist) is shown. In Table 5 the IC_{50} values are expressed as: +++ = IC_{50} of <10 μM; ++ = IC_{50} of 10-50 μM; + = IC_{50} of 50-100 μM (μM = micromolar).

Table A

Example Number	Platelet Aggregation Assay IC_{50} (without esterase)	Platelet Aggregation Assay IC_{50} (with esterase)
1	+++	
4 (isomer A)	++	
4 (isomer B)	++	
6	+++	
7	>100	
8	+	
9 (isomer A)	+++	
9 (isomer B)	+++	
33	>100	
43	+++	
89		+++
115		+++
119A (3R)		+++
119B (3S)		+++
120A (3R)		+++
120B (3S)		+++
120C (3R)††		+++
166		+++
189	>100	
190	+	

1337	4-piperidinylmethyl-aminocarbonyl	n-butyloxycarbonyl	OH
1338	4-piperidinylmethyl-amino-carbonyl	n-butyloxycarbonyl	OMe
1339	4-piperidinylmethyl-amino-carbonyl	benzyloxycarbonyl	OH
1340	4-piperidinylmethyl-amino-carbonyl	benzyloxycarbonyl	OMe
1341	4-piperidinylmethyl-amino-carbonyl	n-butylsulfonyl	OH
1342	4-piperidinylmethyl-amino-carbonyl	n-butylsulfonyl	OMe
1343	4-piperidinylmethyl-amino-carbonyl	2-methylphenyl-sulfonyl	OH
1344	4-piperidinylmethyl-amino-carbonyl	2-methylphenyl-sulfonyl	OMe
1345	4-piperidinylmethyl-amino-carbonyl	3-methylphenyl-sulfonyl	OH
1346	4-piperidinylmethyl-amino-carbonyl	4-methylphenyl-sulfonyl	OH
1347	4-piperidinylmethyl-amino-carbonyl	3-methylphenyl-sulfonyl	OMe
1348	4-piperidinylmethyl-amino-carbonyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1349	4-piperidinylmethyl-amino-carbonyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1350	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	n-butyloxycarbonyl	OH
1351	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	n-butyloxycarbonyl	OMe
1352	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	benzyloxycarbonyl	OH
1353	N-(4-piperidiny-methyl)-N-methyl-aminocarbonyl	benzyloxycarbonyl	OMe
1354	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	n-butylsulfonyl	OH
1355	N-(4-piperidinyl-methyl)-N-methylaminocarbonyl	n-butylsulfonyl	OMe
1356	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	2-methylphenyl-sulfonyl	OH
1357	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	2-methylphenyl-sulfonyl	OMe
1358	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3-methylphenyl-sulfonyl	OH
1359	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	4-methylphenyl-sulfonyl	OH
1360	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3-methylphenyl-sulfonyl	OMe

1361	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1362	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1363	4-piperidinyl-aminocarbonyl	n-butyloxycarbonyl	OH
1364	4-piperidinyl-aminocarbonyl	4-methylphenyl-sulfonyl	OH
1365	4-guanidinophenyl	2-methylphenyl-sulfonyl	OH
1366	4-guanidinophenyl	2-methylphenyl-sulfonyl	OMe
1367	4-guanidinophenyl	2-bromophenylsulfonyl	OH
1368	4-guanidinophenyl	2-bromophenylsulfonyl	OMe
1369	4-guanidinophenyl	3-methylphenyl-sulfonyl	OH
1370	4-guanidinophenyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1371	4-guanidinophenyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1372	4-guanidinophenyl	2,4-dimethyl-thiazolylsulfonyl	OH
1373	4-guanidinophenyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1374	4-guanidinophenyl	benzylsulfonyl	OH
1375	4-guanidinophenyl	benzylsulfonyl	OMe
1376	4-guanidinophenyl	styrylsulfonyl	OH
1377	4-guanidinophenyl	styrylsulfonyl	OMe
1378	4-guanidinophenyl	2-benzothiophene-sulfonyl	OH
1379	3-guanidinophenyl	n-butyloxycarbonyl	OH
1380	3-guanidinophenyl	n-butyloxycarbonyl	OMe
1381	3-guanidinophenyl	n-propyloxycarbonyl	OH
1382	3-guanidinophenyl	2-bromophenylsulfonyl	OH
1383	3-guanidinophenyl	2-bromophenylsulfonyl	OMe
1384	3-guanidinophenyl	2-methylphenyl-sulfonyl	OH
1385	3-guanidinophenyl	4-methylphenyl-sulfonyl	OH
1386	3-guanidinophenyl	4-methylphenyl-sulfonyl	OMe
1387	3-guanidinophenyl	n-butylsulfonyl	OH
1388	3-guanidinophenyl	n-butylsulfonyl	OMe
1389	3-guanidinophenyl	styrylsulfonyl	OH
1390	3-guanidinophenyl	benzyloxycarbonyl	OH
1391	3-guanidinophenyl	benzyloxycarbonyl	OMe
1392	4-amidinophenylmethyl	2-methylphenyl-sulfonyl	OH
1393	4-amidinophenylmethyl	2-methylphenyl-sulfonyl	OMe
1394	4-amidinophenylmethyl	phenylsulfonyl	OH
1395	4-amidinophenylmethyl	phenylsulfonyl	OMe
1396	4-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1397	4-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1398	4-amidinophenylmethyl	2,4-dimethyl-thiazolylsulfonyl	OH

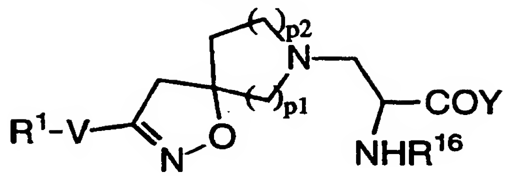
1399	4-amidinophenylmethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1400	4-amidinophenylmethyl	p-toluylsulfonyl	OH
1401	3-amidinophenylmethyl	n-butyloxycarbonyl	OH
1402	3-amidinophenylmethyl	n-butyloxycarbonyl	OMe
1403	3-amidinophenylmethyl	phenylsulfonyl	OH
1404	3-amidinophenylmethyl	phenylsulfonyl	OMe
1405	3-amidinophenylmethyl	2-bromophenylsulfonyl	OH
1406	3-amidinophenylmethyl	2-bromophenylsulfonyl	OMe
1407	3-amidinophenylmethyl	2-methylphenyl-sulfonyl	OH
1408	3-amidinophenylmethyl	2-methylphenyl-sulfonyl	OMe
1409	3-amidinophenylmethyl	4-methylphenyl-sulfonyl	OH
1410	3-amidinophenylmethyl	4-methylphenyl-sulfonyl	OMe
1411	3-amidinophenylmethyl	styrylsulfonyl	OH
1412	3-amidinophenylmethyl	styrylsulfonyl	OMe
1413	3-amidinophenylmethyl	benzyloxycarbonyl	OH
1414	3-amidinophenylmethyl	benzyloxycarbonyl	OMe
1415	3-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1416	3-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1417	3-amidinophenylmethyl	2,4-dimethyl-thiazolylsulfonyl	OH
1418	3-amidinophenylmethyl	benzylsulfonyl	OH
1419	4-pyridylethyl	n-benzyloxycarbonyl	OMe
1420	4-pyridylethyl	n-benzyloxycarbonyl	OH
1421	4-pyridylethyl	n-butyloxyoxycarbonyl	OMe
1422	4-pyridylethyl	n-butyloxyoxycarbonyl	OH
1423	4-pyridylethyl	2-methylphenylsulfonyl	OH
1424	4-pyridylethyl	2-methylphenyl-sulfonyl	OMe
1425	4-pyridylethyl	2-bromophenylsulfonyl	OH
1426	4-pyridylethyl	2-bromophenylsulfonyl	OMe
1427	4-pyridylethyl	3-methylphenyl-sulfonyl	OH
1428	4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1429	4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1430	4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH
1431	4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1432	4-pyridylethyl	benzylsulfonyl	OH
1433	4-pyridylethyl	styrylsulfonyl	OH
1434	4-pyridylethyl	styrylsulfonyl	OMe
1435	4-pyridylethyl	2-benzothiophene-sulfonyl	OH
1436	3-pyridylethyl	n-benzyloxycarbonyl	OMe
1437	3-pyridylethyl	n-benzyloxycarbonyl	OH
1438	3-pyridylethyl	n-butyloxyoxycarbonyl	OMe
1439	3-pyridylethyl	n-butyloxyoxycarbonyl	OH
1440	3-pyridylethyl	2-methylphenyl-sulfonyl	OH
1441	3-pyridylethyl	2-methylphenyl-sulfonyl	OMe
1442	3-pyridylethyl	2-bromophenylsulfonyl	OH

1443	3-pyridylethyl	2-bromophenylsulfonyl	OMe
1444	3-pyridylethyl	3-methylphenyl-sulfonyl	OH
1445	3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1446	3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1447	3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH
1448	3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1449	3-pyridylethyl	benzylsulfonyl	OH
1450	3-pyridylethyl	styrylsulfonyl	OH
1451	3-pyridylethyl	styrylsulfonyl	OMe
1452	3-pyridylethyl	2-benzothiophene-sulfonyl	OH
1453	2-amino-4-pyridylethyl	n-benzyloxycarbonyl	OMe
1454	2-amino-4-pyridylethyl	n-benzyloxycarbonyl	OH
1455	2-amino-4-pyridylethyl	n-butyloxyoxycarbonyl	OMe
1456	2-amino-4-pyridylethyl	n-butyloxyoxycarbonyl	OH
1457	2-amino-4-pyridylethyl	2-methylphenyl-sulfonyl	OH
1458	2-amino-4-pyridylethyl	2-methylphenyl-sulfonyl	OMe
1459	2-amino-4-pyridylethyl	2-bromophenylsulfonyl	OH
1460	2-amino-4-pyridylethyl	2-bromophenylsulfonyl	OMe
1461	2-amino-4-pyridylethyl	3-methylphenyl-sulfonyl	OH
1462	2-amino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1463	2-amino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1464	2-amino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH
1465	2-amino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1466	2-amino-4-pyridylethyl	benzylsulfonyl	OH
1467	2-amino-4-pyridylethyl	benzylsulfonyl	OMe
1468	2-amino-4-pyridylethyl	styrylsulfonyl	OH
1469	2-amino-4-pyridylethyl	styrylsulfonyl	OMe
1470	2-amino-4-pyridylethyl	2-benzothiophene-sulfonyl	OH
1471	6-amino-3-pyridylethyl	n-benzyloxycarbonyl	OMe
1472	6-amino-3-pyridylethyl	n-benzyloxycarbonyl	OH
1473	6-amino-3-pyridylethyl	n-butyloxyoxycarbonyl	OMe
1474	6-amino-3-pyridylethyl	n-butyloxyoxycarbonyl	OH
1475	6-amino-3-pyridylethyl	2-methylphenyl-sulfonyl	OH
1476	6-amino-3-pyridylethyl	2-methylphenyl-sulfonyl	OMe
1477	6-amino-3-pyridylethyl	2-bromophenylsulfonyl	OH
1478	6-amino-3-pyridylethyl	2-bromophenylsulfonyl	OMe
1479	6-amino-3-pyridylethyl	3-methylphenyl-sulfonyl	OH
1480	6-amino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1481	6-amino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1482	6-amino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH

1483	6-amino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1484	6-amino-3-pyridylethyl	benzylsulfonyl	OH
1485	6-amino-3-pyridylethyl	benzylsulfonyl	OMe
1486	6-amino-3-pyridylethyl	styrylsulfonyl	OH
1487	6-amino-3-pyridylethyl	styrylsulfonyl	OMe
1488	6-amino-4-pyridylethyl	2-benzothiophene-sulfonyl	OH
1489	2-amidino-4-pyridylethyl	n-benzyloxycarbonyl	OMe
1490	2-amidino-4-pyridylethyl	n-benzyloxycarbonyl	OH
1491	2-amidino-4-pyridylethyl	n-butyloxyoxycarbonyl	OMe
1492	2-amidino-4-pyridylethyl	n-butyloxyoxycarbonyl	OH
1493	2-amidino-4-pyridylethyl	2-methylphenyl-sulfonyl	OH
1494	2-amidino-4-pyridylethyl	2-methylphenyl-sulfonyl	OMe
1495	2-amidino-4-pyridylethyl	2-bromophenylsulfonyl	OH
1496	2-amidino-4-pyridylethyl	2-bromophenylsulfonyl	OMe
1497	2-amidino-4-pyridylethyl	3-methylphenyl-sulfonyl	OH
1498	2-amidino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH
1499	2-amidino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe
1500	2-amidino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH
1501	2-amidino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe
1502	2-amidino-4-pyridylethyl	benzylsulfonyl	OH
1503	2-amidino-4-pyridylethyl	benzylsulfonyl	OMe
1504	2-amidino-4-pyridylethyl	styrylsulfonyl	OH
1505	2-amidino-4-pyridylethyl	styrylsulfonyl	OMe
1506	2-amidino-4-pyridylethyl	2-benzothiophene-sulfonyl	OH
1507	6-amidino-3-pyridylethyl	n-benzyloxycarbonyl	OMe
1508	6-amidino-3-pyridylethyl	n-benzyloxycarbonyl	OH
1509	6-amidino-3-pyridylethyl	n-butyloxyoxycarbonyl	OMe
1510	6-amidino-3-pyridylethyl	n-butyloxyoxycarbonyl	OH
1511	6-amidino-3-pyridylethyl	2-methylphenyl-sulfonyl	OH
1512	6-amidino-3-pyridylethyl	2-methylphenyl-sulfonyl	OMe
1513	6-amidino-3-pyridylethyl	2-bromophenylsulfonyl	OH
1514	6-amidino-3-pyridylethyl	2-bromophenylsulfonyl	OMe

1515	6-amidino-3-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1516	6-amidino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1517	6-amidino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1518	6-amidino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1519	6-amidino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1520	6-amidino-3-pyridylethyl	benzylsulfonyl	OH	
1521	6-amidino-3-pyridylethyl	benzylsulfonyl	Me	
1522	6-amidino-3-pyridylethyl	styrylsulfonyl	OH	
1523	6-amidino-3-pyridylethyl	styrylsulfonyl	OMe	
1524	6-amidino-3-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1525	guanidinoethyl	benzyloxycarbonyl	OH	421

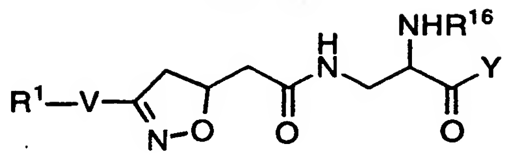
Table 8



Ex. No.	R^1-V	p^1	p^2	R^{16}	Y	MS M+H
1540	4-amidinophenyl	2	1	*n*-butyloxycarbonyl	OH	446
1541	4-amidinophenyl	2	1	3-methylphenylsulfonyl	OH	448
1542	4-amidinophenyl	1	1	benzyloxycarbonyl	OMe	
1543	4-amidinophenyl	1	1	(2-methylphenyl)-methoxycarbonyl	OH	
1544	4-amidinophenyl	1	1	(3-methylphenyl)-methoxycarbonyl	OH	
1545	4-amidinophenyl	1	2	*i*-butyloxycarbonyl	OMe	
1546	4-amidinophenyl	1	2	4-methylphenylsulfonyl	OH	
1547	4-amidinophenyl	1	2	2-methylphenylsulfonyl	OH	
1548	4-amidinophenyl	2	1	3,5-dimethylpyrazoyl-sulfonyl	OH	
1549	4-amidinophenyl	2	1	3,5-dimethylisoxazoyl-sulfonyl	OH	
1550	4-amidinophenyl	2	1	*i*-butylaminosulfonyl	OH	
1551	4-amidinophenyl	2	1	2-bromophenylsulfonyl	OH	
1552	4-piperidinylethyl	1	1	*n*-propyloxycarbonyl	OMe	
1553	4-piperidinylethyl	1	2	*n*-butylsulfonyl	OH	
1554	4-piperidinylethyl	1	2	(3-bromophenyl)-methylsulfonyl	OH	
1555	4-piperidinylethyl	2	1	(3-methylphenyl)-methoxycarbonyl	OMe	
1556	4-piperidinylethyl	2	1	2-phenylethoxycarbonyl	OH	
1557	4-(N-benzylamid-ino)phenyl	1	1	*n*-butyloxycarbonyl	OH	
1558	4-[N-(2-methylphenyl)-methylamidino]phenyl	1	1	3-methylphenylsulfonyl	OH	
1559	4-[N-(2-bromophenyl)-methylamidino]phenyl	1	2	2-bromophenylsulfonyl	OH	

1560	4-(N-butylamidino)-phenyl	2	1	3,5-dimethylpyrazoyl-sulfonyl	OH
1561	4-[N-(2-methoxyphenyl)-methylamidino]phenyl	2	1	3-methylphenylsulfonyl	OH
1562	4-[N-(3-[trifluoro-methyl]phenyl)methyl-amidino]phenyl	2	1	2,5-dimethylthiazolyl-sulfonyl	OH
1563	4-amidino-2-fluoro-phenyl	1	1	3-methylphenylsulfonyl	OH
1564	4-amidino-2-fluoro-phenyl	1	2	*i*-butylaminosulfonyl	
1565	4-amidino-2-fluoro-phenyl	2	1	3,5-dimethylisoxazoyl-sulfonyl	OH
1566	5-amidino-2-pyridyl	1	1	*n*-butyloxycarbonyl	OMe
1567	5-amidino-2-pyridyl	1	2	2-methylphenylsulfonyl	OH
1568	5-amidino-2-pyridyl	1	2	3-methylphenylsulfonyl	OMe
1569	5-amidino-2-pyridyl	2	1	*n*-butylsulfonyl	OH
1570	5-amidino-2-pyridyl	2	1	3,5-dimethylisoxazoyl-sulfonyl	OH
1571	2-amidino-5-pyridyl	1	1	2-bromophenylsulfonyl	OH
1572	2-amidino-5-pyridyl	1	1	2-(trifluoromethyl)-phenylsulfonyl	OMe
1573	2-amidino-5-pyridyl	1	2	*n*-propylaminocarbonyl	OMe
1574	2-amidino-5-pyridyl	1	2	4-methylphenylsulfonyl	OH
1575	2-amidino-5-pyridyl	2	1	2-fluorophenylsulfonyl	OH

Table 9



Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1585	4-piperidinylethyl	n-butyloxycarbonyl	OMe	441
1585A	4-piperidinylmethyl	n-butyloxycarbonyl	OH	427
1586	4-piperidinylethyl	benzyloxycarbonyl	OMe	
1587	4-piperidinylethyl	n-propyloxycarbonyl	OMe	
1588	4-piperidinylethyl	isobutyloxycarbonyl	OMe	
1589	4-piperidinylethyl	2-methylphenylsulfonyl	OMe	
1590	4-piperidinylethyl	3-methylphenylsulfonyl	OMe	
1591	4-piperidinylethyl	4-methylphenylsulfonyl	OMe	
1592	4-piperidinylethyl	2-bromophenylsulfonyl	OMe	
1593	4-piperidinylethyl	3-bromophenylsulfonyl	OMe	
1594	4-piperidinylethyl	2-methoxyphenyl-sulfonyl	OMe	
1595	4-piperidinylethyl	3-methoxyphenyl-sulfonyl	OMe	
1596	4-piperidinylethyl	3-trifluoromethyl-phenylsulfonyl	OMe	
1597	4-piperidinylethyl	n-propylsulfonyl	OMe	
1598	4-piperidinylethyl	n-butylsulfonyl	OMe	
1599	4-piperidinylethyl	isopropylsulfonyl	OMe	
1600	4-piperidinylethyl	isobutylsulfonyl	OMe	
1601	4-piperidinylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1602	4-piperidinylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1603	4-piperidinylpropyl	n-butyloxycarbonyl	OMe	455
1604	4-piperidinylpropyl	n-propyloxycarbonyl	OMe	
1605	4-piperidinylpropyl	benzyloxycarbonyl	OMe	
1606	4-piperidinylpropyl	isobutyloxycarbonyl	OMe	
1607	4-piperidinylpropyl	2-methylphenyl-sulfonyl	OMe	
1608	4-piperidinylpropyl	3-methylphenyl-sulfonyl	OMe	
1609	4-piperidinylpropyl	4-methylphenyl-sulfonyl	OMe	509
1610	4-piperidinylpropyl	2-bromophenylsulfonyl	OMe	
1611	4-piperidinylpropyl	n-butylsulfonyl	OMe	
1612	4-piperidinylpropyl	isobutylsulfonyl	OMe	
1613	4-piperidinylpropyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1614	4-piperidinylpropyl	2,4-dimethyl-thiazoylsulfonyl	OMe	
1615	4-piperidinylethyl	n-butyloxycarbonyl	OH	
1616	4-piperidinylethyl	n-propyloxycarbonyl	OH	
1617	4-piperidinylethyl	benyloxycarbonyl	OH	
1618	4-piperidinylethyl	isobutyloxycarbonyl	OH	
1619	4-piperidinylethyl	2-methylphenyl-sulfonyl	OH	481

1620	4-piperidinylethyl	3-methylphenyl-sulfonyl	OH	481
1621	4-piperidinylethyl	4-methylphenyl-sulfonyl	OH	481
1622	4-piperidinylethyl	2-bromophenylsulfonyl	OH	545
1623	4-piperidinylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	486
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1624	4-piperidinylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	502
1625	4-piperidinylethyl	n-butylsulfonyl	OH	447
1626	4-piperidinylethyl	isobutylsulfonyl	OH	
1627	4-piperidinylpropyl	n-butyloxycarbonyl	OH	441
1628	4-piperidinylpropyl	n-propyloxycarbonyl	OH	
1629	4-piperidinylpropyl	isobutyloxycarbonyl	OH	
1630	4-piperidinylpropyl	2-methylphenyl-carbonyl	OH	
1631	4-piperidinylpropyl	4-methylphenyl-carbonyl	OH	495
1632	4-piperidinylpropyl	2-bromophenyl-carbonyl	OH	
1633	4-piperidinylpropyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1634	4-piperidinylpropyl	n-butylsulfonyl	OH	
1635	4-piperidinylpropyl	isobutylsulfonyl	OH	
1636	4-amidinopiperidinyl	n-butyloxycarbonyl	OMe	
1637	4-amidinopiperidinyl	isobutyloxycarbonyl	OMe	
1638	4-amidinopiperidinyl	n-propyloxycarbonyl	OMe	
1639	4-amidinopiperidinyl	benzyloxycarbonyl	OMe	
1640	4-amidinopiperidinyl	n-butylsulfonyl	OMe	
1641	4-amidinopiperidinyl	isobutylsulfonyl	OMe	
1642	4-amidinopiperidinyl	n-propylsulfonyl	OMe	
1643	4-amidinopiperidinyl	2-methylphenyl-sulfonyl	OMe	
1644	4-amidinopiperidinyl	4-methylphenyl-sulfonyl	OMe	
1645	4-amidinopiperidinyl	benzylsulfonyl	OMe	
1646	4-amidinopiperidinyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1647	4-amidinopiperidinyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1648	4-amidinopiperidinyl	4-methylphenyl-sulfonyl	OH	
1649	4-amidinopiperidinyl	n-butyloxycarbonyl	OH	
1650	4-amidinopiperidinyl	isobutyloxycarbonyl	OH	
1651	4-amidinopiperidinyl	n-propyloxycarbonyl	OH	
1652	4-amidinopiperidinyl	benzyloxycarbonyl	OH	
1653	4-amidinopiperidinyl	n-butylsulfonyl	OH	
1654	4-amidinopiperidinyl	isobutylsulfonyl	OH	
1655	4-amidinopiperidinyl	2-methylphenyl-sulfonyl	OH	
1656	4-amidinopiperidinyl	3-methylphenyl-sulfonyl	OH	495
1657	4-amidinopiperidinyl	4-methylphenyl-sulfonyl	OH	495
1658	4-amidinopiperidinyl	2-bromophenylsulfonyl	OH	
1659	4-amidinopiperidinyl	3-bromophenylsulfonyl	OH	
1660	4-amidinopiperidinyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1661	4-amidinopiperidinyl	2,4-dimethyl-thiazolylsulfonyl	OH	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
1662	4-amidino-piperidinylmethyl	n-butyloxycarbonyl	OMe	427
1663	4-amidino-piperidinylmethyl	n-propyloxycarbonyl	OMe	
1664	4-amidino-piperidinylmethyl	benzyloxycarbonyl	OMe	
1665	4-amidino-piperidinylmethyl	n-butylsulfonyl	OMe	
1666	4-amidino-piperidinylmethyl	n-propylsulfonyl	OMe	
1667	4-amidino-piperidinylmethyl	2-methylphenyl-sulfonyl	OMe	
1668	4-amidino-piperidinylmethyl	3-methylphenyl-sulfonyl	OMe	
1669	4-amidino-piperidinylmethyl	4-methylphenyl-sulfonyl	OMe	
1670	4-amidino-piperidinylmethyl	2-bromophenylsulfonyl	OMe	
1671	4-amidino-piperidinylmethyl	3-bromophenylsulfonyl	OMe	
1672	4-amidino-piperidinylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1673	4-amidino-piperidinylmethyl	4-methylphenyl-sulfonyl	OH	509
1674	4-amidino-piperidinylmethyl	n-butyloxycarbonyl	OH	
1675	4-amidino-piperidinylmethyl	n-propyloxycarbonyl	OH	
1676	4-amidino-piperidinylmethyl	benzyloxycarbonyl	OH	
1677	4-amidino-piperidinylmethyl	n-butylsulfonyl	OH	
1678	4-amidino-piperidinylmethyl	2-methylphenyl-sulfonyl	OH	
1679	4-amidino-piperidinylmethyl	3-methylphenyl-sulfonyl	OH	
1680	4-amidino-piperidinylmethyl	2-bromophenyl-sulfonyl	OH	
1681	4-amidino-piperidinylmethyl	3-bromophenyl-sulfonyl	OH	
1682	4-amidino-piperidinylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1683	4-quinuclidinylethyl	n-butyloxycarbonyl	OH	
1684	4-quinuclidinylethyl	n-propyloxycarbonyl	OH	
1685	4-quinuclidinylethyl	benzyloxycarbonyl	OH	
1686	4-quinuclidinylethyl	n-butylsulfonyl	OH	
1687	4-quinuclidinylethyl	2-methylphenyl-sulfonyl	OH	
1688	4-quinuclidinylethyl	4-methylphenyl-sulfonyl	OH	
1689	4-quinuclidinylethyl	2-bromophenylsulfonyl	OH	
1690	4-quinuclidinylethyl	3-bromophenylsulfonyl	OH	
1691	4-quinuclidinylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1692	guanidinopropyl	n-butyloxycarbonyl	OMe	
1693	guanidinopropyl	n-propyloxycarbonyl	OMe	
1694	guanidinopropyl	benzyloxycarbonyl	OH	449
1695	guanidinopropyl	n-butylsulfonyl	OMe	

1696	guanidinopropyl	2-methylphenyl-sulfonyl	OMe	
1697	guanidinopropyl	3-methylphenyl-sulfonyl	OMe	
1698	guanidinopropyl	2-bromophenylsulfonyl	OMe	
1699	guanidinopropyl	3-bromophenylsulfonyl	OMe	
1700	guanidinopropyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1701	guanidinopropyl	benzylsulfonyl	OMe	
1702	guanidinopropyl	styrylsulfonyl	OMe	
1703	guanidinopropyl	2-benzothiophene-sulfonyl	OMe	
1704	guanidinopropyl	n-butyloxycarbonyl	OH	529
1705	guanidinopropyl	n-propyloxycarbonyl	OH	
1706	guanidinopropyl	benzyloxycarbonyl	OH	
1707	guanidinopropyl	n-butylsulfonyl	OH	
1708	guanidinopropyl	2-methylphenyl-sulfonyl	OH	
1709	guanidinopropyl	3-methylphenyl-sulfonyl	OH	
1710	guanidinopropyl	4-methylphenyl-sulfonyl	OH	
1711	guanidinopropyl	2-bromophenylsulfonyl	OH	
1712	guanidinopropyl	3-bromophenylsulfonyl	OH	
1713	guanidinopropyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1714	guanidinopropyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1715	guanidinopropyl	benzylsulfonyl	OH	
1716	guanidinopropyl	styrylsulfonyl	OH	
1717	guanidinopropyl	2-benzothiophene-sulfonyl	OH	
1718	guanidinobutyl	n-butyloxycarbonyl	OH	
1719	guanidinobutyl	n-butylsulfonyl	OH	
1720	guanidinobutyl	phenylsulfonyl	OH	
1721	guanidinobutyl	2-methylphenyl-sulfonyl	OH	
1722	guanidinobutyl	4-methylphenyl-sulfonyl	OH	
1723	guanidinobutyl	2-bromophenylsulfonyl	OH	
1724	guanidinobutyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1725	guanidinobutyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1726	guanidinobutyl	benzylsulfonyl	OH	
1727	guanidinobutyl	styrylsulfonyl	OH	
1728	guanidinobutyl	3-fluorophenyl-sulfonyl	OH	
1729	guanidinobutyl	n-butyloxycarbonyl	OMe	
1730	guanidinobutyl	n-butylsulfonyl	OMe	
1731	guanidinobutyl	benzyloxycarbonyl	OH	463
1732	guanidinobutyl	phenylsulfonyl	OMe	
1733	guanidinobutyl	2-methylphenyl-sulfonyl	OMe	
1734	guanidinobutyl	2-bromophenylsulfonyl	OMe	
1735	guanidinobutyl	3-bromophenylsulfonyl	OMe	
1736	guanidinobutyl	3,5-dimethyl-isoxazolyl sufonyl	OMe	
1737	guanidinobutyl	benzylsulfonyl	OMe	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
1738	guanidinobutyl	n-butyloxycarbonyl	OH	
1739	guanidinobutyl	isobutyloxycarbonyl	OH	
1740	guanidinobutyl	n-propyloxycarbonyl	OH	
1741	guanidinobutyl	phenylsulfonyl	OH	
1742	guanidinobutyl	n-butylsulfonyl	OH	
1743	guanidinobutyl	2-methylphenyl-sulfonyl	OH	
1744	guanidinobutyl	3-methylphenyl-sulfonyl	OH	
1745	guanidinobutyl	4-methylphenyl-sulfonyl	OH	
1746	guanidinobutyl	2-bromophenylsulfonyl	OH	
1747	4-piperidinylmethyl-aminocarbonyl	n-butyloxycarbonyl	OH	
1748	4-piperidinylmethyl-amino-carbonyl	n-butyloxycarbonyl	OMe	
1749	4-piperidinylmethyl-amino-carbonyl	benzyloxycarbonyl	OH	
1750	4-piperidinylmethyl-amino-carbonyl	benzyloxycarbonyl	OMe	
1751	4-piperidinylmethyl-amino-carbonyl	n-butylsulfonyl	OH	
1752	4-piperidinylmethyl-amino-carbonyl	n-butylsulfonyl	OMe	
1753	4-piperidinylmethyl-amino-carbonyl	2-methylphenyl-sulfonyl	OH	
Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
1754	4-piperidinylmethyl-amino-carbonyl	2-methylphenyl-sulfonyl	OMe	
1755	4-piperidinylmethyl-amino-carbonyl	3-methylphenyl-sulfonyl	OH	
1756	4-piperidinylmethyl-amino-carbonyl	4-methylphenyl-sulfonyl	OH	510
1757	4-piperidinylmethyl-amino-carbonyl	3-methylphenyl-sulfonyl	OMe	
1758	4-piperidinylmethyl-amino-carbonyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1759	4-piperidinylmethyl-amino-carbonyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1760	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	n-butyloxycarbonyl	OH	
1761	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	n-butyloxycarbonyl	OMe	
1762	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	benzyloxycarbonyl	OH	
1763	N-(4-piperidiny-methyl)-N-methyl-aminocarbonyl	benzyloxycarbonyl	OMe	
1764	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	n-butylsulfonyl	OH	
1765	N-(4-piperidinyl-methyl)-N-methylaminocarbonyl	n-butylsulfonyl	OMe	
1766	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	2-methylphenyl-sulfonyl	OH	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1767	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	2-methylphenyl-sulfonyl	OMe	
1768	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3-methylphenyl-sulfonyl	OH	
1769	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	4-methylphenyl-sulfonyl	OH	524
1770	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3-methylphenyl-sulfonyl	OMe	
1771	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1772	N-(4-piperidinyl-methyl)-N-methyl-aminocarbonyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1773	4-piperidinyl-aminocarbonyl	n-butyloxycarbonyl	OH	
1774	4-piperidinyl-aminocarbonyl	4-methylphenyl-sulfonyl	OH	496
1775	4-guanidinophenyl	2-methylphenyl-sulfonyl	OH	
1776	4-guanidinophenyl	2-methylphenyl-sulfonyl	OMe	
1777	4-guanidinophenyl	2-bromophenylsulfonyl	OH	
1778	4-guanidinophenyl	2-bromophenylsulfonyl	OMe	
1779	4-guanidinophenyl	3-methylphenyl-sulfonyl	OH	
1780	4-guanidinophenyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1781	4-guanidinophenyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1782	4-guanidinophenyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1783	4-guanidinophenyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1784	4-guanidinophenyl	benzylsulfonyl	OH	
1785	4-guanidinophenyl	benzylsulfonyl	OMe	
1786	4-guanidinophenyl	styrylsulfonyl	OH	
1787	4-guanidinophenyl	styrylsulfonyl	OMe	
1788	4-guanidinophenyl	2-benzothiophene-sulfonyl	OH	
1789	3-guanidinophenyl	n-butyloxycarbonyl	OH	
1790	3-guanidinophenyl	n-butyloxycarbonyl	OMe	
1791	3-guanidinophenyl	n-propyloxycarbonyl	OH	
1792	3-guanidinophenyl	2-bromophenylsulfonyl	OH	
1793	3-guanidinophenyl	2-bromophenylsulfonyl	OMe	
1794	3-guanidinophenyl	2-methylphenyl-sulfonyl	OH	
1795	3-guanidinophenyl	4-methylphenyl-sulfonyl	OH	
1796	3-guanidinophenyl	4-methylphenyl-sulfonyl	OMe	
1797	3-guanidinophenyl	n-butylsulfonyl	OH	
1798	3-guanidinophenyl	n-butylsulfonyl	OMe	
1799	3-guanidinophenyl	styrylsulfonyl	OH	
1800	3-guanidinophenyl	benzyloxycarbonyl	OH	

1801	3-guanidinophenyl	benzyloxycarbonyl	OMe	
1802	4-amidinophenylmethyl	2-methylphenyl-sulfonyl	OH	
1803	4-amidinophenylmethyl	2-methylphenyl-sulfonyl	OMe	
1804	4-amidinophenylmethyl	phenylsulfonyl	OH	
1805	4-amidinophenylmethyl	phenylsulfonyl	OMe	
1806	4-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1807	4-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1808	4-amidinophenylmethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1809	4-amidinophenylmethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1810	4-amidinophenylmethyl	p-toluylsulfonyl	OH	
Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
1811	3-amidinophenylmethyl	n-butyloxycarbonyl	OH	
1812	3-amidinophenylmethyl	n-butyloxycarbonyl	OMe	
1813	3-amidinophenylmethyl	phenylsulfonyl	OH	
1814	3-amidinophenylmethyl	phenylsulfonyl	OMe	
1815	3-amidinophenylmethyl	2-bromophenylsulfonyl	OH	
1816	3-amidinophenylmethyl	2-bromophenylsulfonyl	OMe	
1817	3-amidinophenylmethyl	2-methylphenyl-sulfonyl	OH	
1818	3-amidinophenylmethyl	2-methylphenyl-sulfonyl	OMe	
1819	3-amidinophenylmethyl	4-methylphenyl-sulfonyl	OH	
1820	3-amidinophenylmethyl	4-methylphenyl-sulfonyl	OMe	
1821	3-amidinophenylmethyl	styrylsulfonyl	OH	
1822	3-amidinophenylmethyl	styrylsulfonyl	OMe	
1823	3-amidinophenylmethyl	benzyloxycarbonyl	OH	
1824	3-amidinophenylmethyl	benzyloxycarbonyl	OMe	
1825	3-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1826	3-amidinophenylmethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1827	3-amidinophenylmethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1828	3-amidinophenylmethyl	benzylsulfonyl	OH	
1829	4-pyridylethyl	n-benzyloxycarbonyl	OMe	
1830	4-pyridylethyl	n-benzyloxycarbonyl	OH	
1831	4-pyridylethyl	n-butyloxyoxycarbonyl	OMe	
1832	4-pyridylethyl	n-butyloxyoxycarbonyl	OH	
1833	4-pyridylethyl	2-methylphenylsulfonyl	OH	
1834	4-pyridylethyl	2-methylphenyl-sulfonyl	OMe	
1835	4-pyridylethyl	2-bromophenylsulfonyl	OH	
1836	4-pyridylethyl	2-bromophenylsulfonyl	OMe	
1837	4-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1838	4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1839	4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1840	4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
1841	4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1842	4-pyridylethyl	benzylsulfonyl	OH	
1843	4-pyridylethyl	styrylsulfonyl	OH	
1844	4-pyridylethyl	styrylsulfonyl	OMe	
1845	4-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1846	3-pyridylethyl	n-benzyloxycarbonyl	OMe	
1847	3-pyridylethyl	n-benzyloxycarbonyl	OH	
1848	3-pyridylethyl	n-butyloxyoxycarbonyl	OMe	
1849	3-pyridylethyl	n-butyloxyoxycarbonyl	OH	
1850	3-pyridylethyl	2-methylphenyl-sulfonyl	OH	
1851	3-pyridylethyl	2-methylphenyl-sulfonyl	OMe	
1852	3-pyridylethyl	2-bromophenylsulfonyl	OH	
1853	3-pyridylethyl	2-bromophenylsulfonyl	OMe	
1854	3-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1855	3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1856	3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1857	3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1858	3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1859	3-pyridylethyl	benzylsulfonyl	OH	
1860	3-pyridylethyl	styrylsulfonyl	OH	
1861	3-pyridylethyl	styrylsulfonyl	OMe	
1862	3-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1863	2-amino-4-pyridylethyl	n-benzyloxycarbonyl	OMe	
1864	2-amino-4-pyridylethyl	n-benzyloxycarbonyl	OH	
1865	2-amino-4-pyridylethyl	n-butyloxyoxycarbonyl	OMe	
1866	2-amino-4-pyridylethyl	n-butyloxyoxycarbonyl	OH	
1867	2-amino-4-pyridylethyl	2-methylphenyl-sulfonyl	OH	
1868	2-amino-4-pyridylethyl	2-methylphenyl-sulfonyl	OMe	
1869	2-amino-4-pyridylethyl	2-bromophenylsulfonyl	OH	
1870	2-amino-4-pyridylethyl	2-bromophenylsulfonyl	OMe	
1871	2-amino-4-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1872	2-amino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1873	2-amino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1874	2-amino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1875	2-amino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1876	2-amino-4-pyridylethyl	benzylsulfonyl	OH	
1877	2-amino-4-pyridylethyl	benzylsulfonyl	OMe	
1878	2-amino-4-pyridylethyl	styrylsulfonyl	OH	
1879	2-amino-4-pyridylethyl	styrylsulfonyl	OMe	
1880	2-amino-4-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1881	6-amino-3-pyridylethyl	n-benzyloxycarbonyl	OMe	

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1882	6-amino-3-pyridylethyl	n-benzyloxycarbonyl	OH	
1883	6-amino-3-pyridylethyl	n-butyloxyoxycarbonyl	OMe	
1884	6-amino-3-pyridylethyl	n-butyloxyoxycarbonyl	OH	
1885	6-amino-3-pyridylethyl	2-methylphenyl-sulfonyl	OH	
1886	6-amino-3-pyridylethyl	2-methylphenyl-sulfonyl	OMe	
1887	6-amino-3-pyridylethyl	2-bromophenylsulfonyl	OH	
1888	6-amino-3-pyridylethyl	2-bromophenylsulfonyl	OMe	
1889	6-amino-3-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1890	6-amino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1891	6-amino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1892	6-amino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1893	6-amino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1894	6-amino-3-pyridylethyl	benzylsulfonyl	OH	
1895	6-amino-3-pyridylethyl	benzylsulfonyl	OMe	
1896	6-amino-3-pyridylethyl	styrylsulfonyl	OH	
1897	6-amino-3-pyridylethyl	styrylsulfonyl	OMe	
1898	6-amino-4-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1899	2-amidino-4-pyridylethyl	n-benzyloxycarbonyl	OMe	
1900	2-amidino-4-pyridylethyl	n-benzyloxycarbonyl	OH	
1901	2-amidino-4-pyridylethyl	n-butyloxyoxycarbonyl	OMe	
1902	2-amidino-4-pyridylethyl	n-butyloxyoxycarbonyl	OH	
1903	2-amidino-4-pyridylethyl	2-methylphenyl-sulfonyl	OH	
1904	2-amidino-4-pyridylethyl	2-methylphenyl-sulfonyl	OMe	
1905	2-amidino-4-pyridylethyl	2-bromophenylsulfonyl	OH	
1906	2-amidino-4-pyridylethyl	2-bromophenylsulfonyl	OMe	
1907	2-amidino-4-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1908	2-amidino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1909	2-amidino-4-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1910	2-amidino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1911	2-amidino-4-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1912	2-amidino-4-pyridylethyl	benzylsulfonyl	OH	
1913	2-amidino-4-pyridylethyl	benzylsulfonyl	OMe	
1914	2-amidino-4-pyridylethyl	styrylsulfonyl	OH	
1915	2-amidino-4-pyridylethyl	styrylsulfonyl	OMe	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
1916	2-amidino-4-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1917	6-amidino-3-pyridylethyl	n-benzyloxycarbonyl	OMe	
1918	6-amidino-3-pyridylethyl	n-benzyloxycarbonyl	OH	
1919	6-amidino-3-pyridylethyl	n-butyloxyoxycarbonyl	OMe	
1920	6-amidino-3-pyridylethyl	n-butyloxyoxycarbonyl	OH	
1921	6-amidino-3-pyridylethyl	2-methylphenyl-sulfonyl	OH	
1922	6-amidino-3-pyridylethyl	2-methylphenyl-sulfonyl	OMe	
1923	6-amidino-3-pyridylethyl	2-bromophenylsulfonyl	OH	
1924	6-amidino-3-pyridylethyl	2-bromophenylsulfonyl	OMe	
1925	6-amidino-3-pyridylethyl	3-methylphenyl-sulfonyl	OH	
1926	6-amidino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OH	
1927	6-amidino-3-pyridylethyl	3,5-dimethyl-isoxazolylsulfonyl	OMe	
1928	6-amidino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OH	
1929	6-amidino-3-pyridylethyl	2,4-dimethyl-thiazolylsulfonyl	OMe	
1930	6-amidino-3-pyridylethyl	benzylsulfonyl	OH	
1931	6-amidino-3-pyridylethyl	benzylsulfonyl	Me	
1932	6-amidino-3-pyridylethyl	styrylsulfonyl	OH	
1933	6-amidino-3-pyridylethyl	styrylsulfonyl	OMe	
1934	6-amidino-3-pyridylethyl	2-benzothiophene-sulfonyl	OH	
1935	4-amidino-2-fluoro-phenyl	2-methylphenylsulfonyl	OH	
1936	4-amidino-2-fluoro-phenyl	3,5-dimethylisoxazolyl-sulfonyl	OH	
1937	2-amidino-5-pyridyl	2-methylphenylsulfonyl	OH	
1938	2-amidino-5-pyridyl	2-bromophenylsulfonyl	OH	
1939	2-amidino-5-pyridyl	*i*-butyloxycarbonyl	OMe	
1940	2-amidino-5-pyridyl	3,5-dimethylisoxazolyl-sulfonyl	OH	
1941	3-amidino-6-pyridyl	2-methylphenylsulfonyl	OH	
1942	3-amidino-6-pyridyl	2-bromophenylsulfonyl	OMe	
1943	3-amidino-6-pyridyl	2,5-dimethylthiazolyl-sulfonyl	OH	
1944	3-amidino-6-pyridyl	3,5-dimethylisoxazolyl-sulfonyl	OH	
1945	4-piperidinylethyl	3-methylphenylsulfonyl	OH	481
1946	4-(N-2-methoxybenzyl)-amidinophenyl HCl	2-methylphenylsulfonyl	OMe	622.3
1947	4-(N-2-methoxybenzyl)-amidinophenyl TFA	2-methylphenylsulfonyl	OH	608.3

1948	4-(N-n-butyl)-amidinophenyl	2-methylphenylsulfonyl	OMe	558.4
1949	4-(N-n-butyl)-amidinophenyl	2-methylphenylsulfonyl	OH	544.4
1950	4-(N-ethyl)-amidinophenyl	2-methylphenylsulfonyl	OMe	530.3
1951	4-(N-ethyl)-amidinophenyl	2-methylphenylsulfonyl	OH	516.3
1952	4-amidinophenoxymethyl	benzyloxycarbonyl	OMe	
1953	4-amidinophenoxymethyl	benzyloxycarbonyl	OH	
1954	4-amidinophenoxymethyl	n-butyloxycarbonyl	OMe	
1955	4-amidinophenoxymethyl	n-butyloxycarbonyl	OH	
1956	4-amidinophenoxymethyl	cyclopropylethoxy carbonyl	OMe	
1957	4-amidinophenoxymethyl	cyclopropylethoxy carbonyl	OH	
1958	4-amidinophenoxymethyl	4-methylphenylsulfonyl	OMe	
1959	4-amidinophenoxymethyl	4-methylphenylsulfonyl	OH	
1960	4-amidinophenoxymethyl	3-methylphenylsulfonyl	OMe	
1961	4-amidinophenoxymethyl	3-methylphenylsulfonyl	OH	
1962	4-amidinophenoxymethyl	n-butylsulfonyl	OMe	
1963	4-amidinophenoxymethyl	n-butylsulfonyl	OH	
1964	4-amidinophenoxy	benzyloxycarbonyl	OMe	
1965	4-amidinophenoxy	benzyloxycarbonyl	OH	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1967	4-amidinophenoxy	n-butyloxycarbonyl	OMe	
1968				
1969	4-amidinophenoxy	n-butyloxycarbonyl	OH	
1970	4-amidinophenoxy	cyclopropylethyoxy carbonyl	OHe	
1971	4-amidinophenoxy	cyclopropylethoxy carbonyl	OH	
1972	4-amidinophenoxy	4-methylphenylsulfonyl	OMe	
1973	4-amidinophenoxy	4-methylphenylsulfonyl	OH	
1974	4-amidinophenoxy	3-methylphenylsulfonyl	OMe	
1975	4-amidinophenoxy	3-methylphenylsulfonyl	OH	
1976	4-amidinophenoxy	n-butylsulfonyl	OMe	
1977	4-amidinophenoxy	n-butylsulfonyl	OH	
1978	4-amidinophenethyl	benzyloxycarbonyl	OMe	
1979	4-amidinophenethyl	benzyloxycarbonyl	OH	
1980	4-amidinophenethyl	n-butyloxycarbonyl	OMe	
1981	4-amidinophenethyl	n-butyloxycarbonyl	OH	
1982	4-amidinophenethyl	cyclopropylethoxy carbonyl	OMe	
1983	4-amidinophenethyl	cyclopropylethoxy carbonyl	OH	
1984	4-amidinophenethyl	4-methylphenylsulfonyl	OMe	
1985	4-amidinophenethyl	4-methylphenylsulfonyl	OH	
1986	4-amidinophenethyl	3-methylphenylsulfonyl	OMe	
1987	4-amidinophenethyl	3-methylphenylsulfonyl	OH	
1988	4-amidinophenethyl	n-butylsulfonyl	OMe	
1989	4-amidinophenethyl	n-butylsulfonyl	OH	
1990	N-(4-amidinophenyl) aminomethyl	benzyloxycarbonyl	OMe	
1991	N-(4-amidinophenyl) aminomethyl	benzyloxycarbonyl	OH	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$

Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
1993	N-(4-amidinophenyl) aminomethyl	n-butyloxycarbonyl	OMe	
1994	N-(4-amidinophenyl) aminomethyl	n-butyloxycarbonyl	OH	
1995	N-(4-amidinophenyl) aminomethyl	cyclopropylethoxy carbonyl	OH	
1996	N-(4-amidinophenyl) aminomethyl	4-methylphenylsulfonyl	OMe	
1997	N-(4-amidinophenyl) aminomethyl	4-methylphenylsulfonyl	OH	
1998	N-(4-amidinophenyl) aminomethyl	3-methylphenylsulfonyl	OMe	
1999	N-(4-amidinophenyl) aminomethyl	3-methylphenylsulfonyl	OH	
2000	N-(4-amidinophenyl) aminomethyl	n-butylsulfonyl	OMe	
2001	N-(4-amidinophenyl) aminomethyl	n-butylsulfonyl	OH	
2002	4-amidinophenyl methylamino	benzyloxycarbonyl	OMe	
2003	4-amidinophenyl methylamino	benzyloxycarbonyl	OH	
2004	4-amidinophenyl methylamino	n-butyloxycarbonyl	OMe	
2005	4-amidinophenyl methylamino	n-butyloxycarbonyl	OH	
2006	4-amidinophenyl methylamino	cyclopropylethoxy carbonyl	OMe	
2007	4-amidinophenyl methylamino	cyclopropylethoxy carbonyl	OH	
2008	4-amidinophenyl methylamino	4-methylphenylsulfonyl	OMe	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
2010	4-amidinophenyl methylamino	4-methylphenylsulfonyl	OH	
2011	4-amidinophenyl methylamino	3-methylphenylsulfonyl	OMe	
2012	4-amidinophenyl methylamino	n-butylsulfonyl	OMe	
2013	4-amidinophenyl methylamino	n-butylsulfonyl	OH	
2014	N-(4-amidinophenyl) aminocarbonyl	benzyloxycarbonyl	OMe	
2015	N-(4-amidinophenyl) aminocarbonyl	benzyloxycarbonyl	OH	
2016	N-(4-amidinophenyl) aminocarbonyl	n-butyloxycarbonyl	OMe	
2017	N-(4-amidinophenyl) aminocarbonyl	n-butyloxycarbonyl	OH	
2018	N-(4-amidinophenyl) aminocarbonyl	cyclopropylethoxy carbonyl	OMe	
2019	N-(4-amidinophenyl) aminocarbonyl	cyclopropylethoxy carbonyl	OH	
2020	N-(4-amidinophenyl) aminocarbonyl	4-methylphenylsulfonyl	OMe	
2021	N-(4-amidinophenyl) aminocarbonyl	4-methylphenylsulfonyl	OH	
2022	N-(4-amidinophenyl) aminocarbonyl	3-methylphenylsulfonyl	OMe	

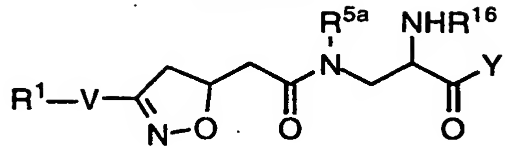
Example Number	R^1—V	R^{16}	Y	MS (M+H)$^+$
2023	N-(4-amidinophenyl) aminocarbonyl	3-methylphenylsulfonyl	OH	
2024	N-(4-amidinophenyl) aminocarbonyl	n-butylsulfonyl	OMe	
2025	N-(4-amidinophenyl) aminocarbonyl	n-butylsulfonyl	OH	
Example Number	R^1—V	R^{16}	Y	MS (M+H)$^+$
2027	4-amidinophenyl carbonylamino	benzyloxycarbonyl	OMe	
2028	4-amidinophenyl carbonylamino	benzyloxycarbonyl	OH	
2029	4-amidinophenyl carbonylamino	n-butyloxycarbonyl	OMe	
2030	4-amidinophenyl carbonylamino	n-butyloxycarbonyl	OH	
2031	4-amidinophenyl carbonylamino	cyclopropylethoxy carbonyl	OMe	
2032	4-amidinophenyl carbonylamino	cyclopropylethoxy carbonyl	OH	
2033	4-amidinophenyl carbonylamino	4-methylphenylsulfonyl	OMe	
2034	4-amidinophenyl carbonylamino	4-methylphenylsulfonyl	OH	
2035	4-amidinophenyl carbonylamino	3-methylphenylsulfonyl	OMe	
2036	4-amidinophenyl carbonylamino	3-methylphenylsulfonyl	OH	
2037	4-amidinophenyl carbonylamino	n-butylsulfonyl	OMe	
2038	4-amidinophenyl carbonylamino	n-butylsulfonyl	OH	
2039	N-(4-amidinophenyl) amino	benzyloxycarbonyl	OMe	
2040	N-(4-amidinophenyl) amino	benzyloxycarbonyl	OH	
2041	N-(4-amidinophenyl) amino	n-butyloxycarbonyl	OMe	
2042	N-(4-amidinophenyl) amino	n-butyloxycarbonyl	OH	
Example Number	R^1—V	R^{16}	Y	MS (M+H)$^+$
2044	N-(4-amidinophenyl) amino	cyclopropylethoxy carbonyl	OMe	
2045	N-(4-amidinophenyl) amino	cyclopropylethoxy carbonyl	OH	
2046	N-(4-amidinophenyl) amino	4-methylphenylsulfonyl	OMe	
2047	N-(4-amidinophenyl) amino	4-methylphenylsulfonyl	OH	
2048	N-(4-amidinophenyl) amino	3-methylphenylsulfonyl	OMe	
2049	N-(4-amidinophenyl) amino	3-methylphenylsulfonyl	OH	
2050	N-(4-amidinophenyl) amino	n-butylsulfonyl	OMe	
2051	N-(4-amidinophenyl) amino	n-butylsulfonyl	OH	
2052	N-(4-amidinophenyl)-N-methylamino	benzyloxycarbonyl	OMe	

2053	N-(4-amidinophenyl)-N-methylamino	benzyloxycarbonyl	OH	
2054	N-(4-amidinophenyl)-N-methylamino	n-butyloxycarbonyl	OMe	
2055	N-(4-amidinophenyl)-N-methylamino	n-butyloxycarbonyl	OH	
2056	N-(4-amidinophenyl)-N-methylamino	cyclopropylethoxy carbonyl	OMe	
2057	N-(4-amidinophenyl)-N-methylamino	cyclopropylethoxy carbonyl	OH	
2058	N-(4-amidinophenyl)-N-methylamino	4-methylphenylsulfonyl	OMe	
2059	N-(4-amidinophenyl)-N-methylamino	4-methylphenylsulfonyl	OH	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
2061	N-(4-amidinophenyl)-N-methylamino	3-methylphenylsulfonyl	OMe	
2062	N-(4-amidinophenyl)-N-methylamino	3-methylphenylsulfonyl	OH	
2063	N-(4-amidinophenyl)-N-methylamino	n-butylsulfonyl	OMe	
2064	N-(4-amidinophenyl)-N-methylamino	n-butylsulfonyl	OH	
2065	4-amidinobenzoyl	benzyloxycarbonyl	OMe	
2066	4-amidinobenzoyl	benzyloxycarbonyl	OH	
2067	4-amidinobenzoyl	n-butyloxycarbonyl	OMe	
2068	4-amidinobenzoyl	n-butyloxycarbonyl	OH	
2069	4-amidinobenzoyl	cyclopropylethoxy carbonyl	OMe	
2070	4-amidinobenzoyl	cyclopropylethoxy carbonyl	OH	
2071	4-amidinobenzoyl	4-methylphenylsulfonyl	OMe	
2072	4-amidinobenzoyl	4-methylphenylsulfonyl	OH	
2073	4-amidinobenzoyl	3-methylphenylsulfonyl	OMe	
2074	4-amidinobenzoyl	3-methylphenylsulfonyl	OH	
2075	4-amidinobenzoyl	n-butylsulfonyl	OMe	
2076	4-amidinobenzoyl	n-butylsulfonyl	OH	
2077	4-amidinophenyl methylcarbonyl	benzyloxycarbonyl	OMe	
2078	4-amidinophenyl methylcarbonyl	benzyloxycarbonyl	OH	
2079	4-amidinophenyl methylcarbonyl	n-butyloxycarbonyl	OMe	
2080	4-amidinophenyl methylcarbonyl	n-butyloxycarbonyl	OH	
2081	4-amidinophenyl methylcarbonyl	cyclopropylethoxy carbonyl	OMe	
Example Number	R^1–V	R^{16}	Y	MS $(M+H)^+$
2083	4-amidinophenyl methylcarbonyl	cyclopropylethoxy carbonyl	OH	
2084	4-amidinophenyl methylcarbonyl	4-methylphenylsulfonyl	OMe	
2085	4-amidinophenyl methylcarbonyl	4-methylphenylsulfonyl	OH	
2086	4-amidinophenyl methylcarbonyl	3-methylphenylsulfonyl	OMe	
2087	4-amidinophenyl methylcarbonyl	3-methylphenylsulfonyl	OH	

Example Number	R^1—V	R^{16}	Y	MS $(M+H)^+$
2088	4-amidinophenyl methylcarbonyl	n-butylsulfonyl	OMe	
2089	4-amidinophenyl methylcarbonyl	n-butylsulfonyl	OH	
2090	4-amidinophenyl-carbonylmethyl	benzyloxycarbonyl	OMe	
2091	4-amidinophenyl-carbonylmethyl	benzyloxycarbonyl	OH	
2092	4-amidinophenyl-carbonylmethyl	n-butyloxycarbonyl	OMe	
2093	4-amidinophenyl-carbonylmethyl	n-butyloxycarbonyl	OH	
2094	4-amidinophenyl-carbonylmethyl	cyclopropylethoxy carbonyl	OMe	
2095	4-amidinophenyl-carbonylmethyl	cyclopropylethoxy carbonyl	OH	
2096	4-amidinophenyl-carbonylmethyl	4-methylphenylsulfonyl	OMe	
2097	4-amidinophenyl-carbonylmethyl	4-methylphenylsulfonyl	OH	
2098	4-amidinophenyl-carbonylmethyl	3-methylphenylsulfonyl	OMe	
2100	4-amidinophenyl-carbonylmethyl	3-methylphenylsulfonyl	OH	
2101	4-amidinophenyl-carbonylmethyl	n-butylsulfonyl	OMe	
2102	4-amidinophenyl-carbonylmethyl	n-butylsulfonyl	OH	
2103	4-amidinophenyl HOAc salt, 5(R),N^2(S) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OMe	HNMR
2104	4-amidinophenyl TFA salt, 5(R),N^2(S) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OH	493
2105	4-amidinophenyl HOAc salt, 5(S),N^2(S) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OMe	HNMR
2106	4-amidinophenyl TFA salt, 5(S),N^2(S) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OH	
2107	4-amidinophenyl HOAc salt, 5(R),N^2(R) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OMe	
2108	4-amidinophenyl HOAc salt, 5(S),N^2(R) isomer	3,5-dimethylisoxazol-4-ylsulfonyl	OMe	
2109	2-guanidinoethyl	carbobenzyloxy	OH	435
2110	5-guanidinovaleryl	carbobenzyloxy	OH	477
2111	4-(N-2-methoxybenyzyl)-amidinophenyl •HCl	2-methylphenylsulfonyl	OMe	622
2112	4-(N-2-methoxybenyzyl)-amidinophenyl •HCl	2-methylphenylsulfonyl	OH	608
2113	4-(N-n-butyl)-amidinophenyl •TFA	2-methylphenylsulfonyl	OMe	558
2114	4-(N-n-butyl)-amidinophenyl •TFA	2-methylphenylsulfonyl	OH	544

2115	4-(N-ethyl)-amidinophenyl •TFA	2-methylphenylsulfonyl	OMe	530
2116	4-(N-ethyl)-amidinophenyl •TFA	2-methylphenylsulfonyl	OH	516
2117	4-amidinophenyl	4-methyl-2-methylcarbonylamino-5-thiazolylsulfonyl •TFA	OH	566
2118	4-amidinophenyl	5-phenylsulfonyl-2-thienylsulfonyl•TFA	OMe	634
2119	4-amidinophenyl	5-phenylsulfonyl-2-thienylsulfonyl•TFA	OMe	620
2120	N-t-butyloxycarbonyl-4-amidinophenyl	5-phenylsulfonyl-2-thienylsulfonyl•TFA	OH	720

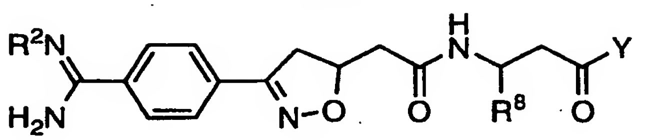
Table 10



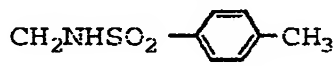
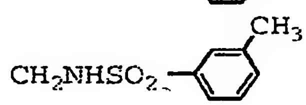
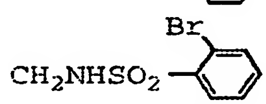
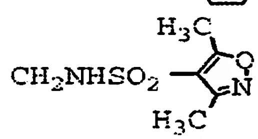
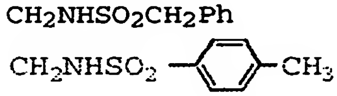
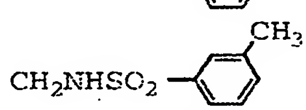
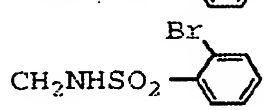
Ex. No.	R^1-V	R^{5a}	R^{16}	Y	MS (M+H)
2121	4-piperidinylethyl	methyl	benzyloxycarbonyl	OH	
2122	4-piperidinylethyl	methyl	2-methylphenylsulfonyl	OH	
2123	4-piperidinylethyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OH	
2124	4-piperidinylethyl	methyl	n-butylsulfonyl	OH	
2125	4-piperidinylethyl	methyl	n-butylsulfonyl	OMe	
2126	4-piperidinylmethyl	methyl	n-butylsulfonyl	OH	
2127	4-piperidinylmethyl	methyl	n-butylsulfonyl	OMe	
2128	4-piperidinylmethyl	methyl	2-methylphenylsulfonyl	OH	
2129	4-piperidinylmethyl	methyl	2-bromophenylsulfonyl	OH	
2130	4-piperidinylmethyl	methyl	3-methylphenylsulfonyl	OH	
2131	4-piperidinylmethyl	methyl	3-methylphenylsulfonyl	OMe	
2132	4-piperidinylmethyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OH	
2133	4-piperidinylmethyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OMe	
2134	4-piperidinylmethyl	methyl	styrylsulfonyl	OH	
2135	4-piperidinylmethyl	methyl	benzyloxycarbonyl	OH	
2136	4-piperidinylmethyl	methyl	benzyloxycarbonyl	OMe	
2137	4-piperidinylmethyl	methyl	n-butyloxycarbonyl	OH	
2138	4-piperidinylmethyl	methyl	n-butyloxycarbonyl	OMe	
2139	4-piperidinylpropyl	methyl	n-butylsulfonyl	OH	
2140	4-piperidinylpropyl	methyl	n-butylsulfonyl	OMe	
2141	4-piperidinylpropyl	methyl	2-methylphenylsulfonyl	OH	
2142	4-piperidinylpropyl	methyl	2-bromophenylsulfonyl	OH	
2143	4-piperidinylpropyl	methyl	3-methylphenylsulfonyl	OH	
2144	4-piperidinylpropyl	methyl	3-methylphenylsulfonyl	OMe	
2145	4-piperidinylpropyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OH	
2146	4-piperidinylpropyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OMe	
2147	4-piperidinylpropyl	methyl	styrylsulfonyl	OH	
2148	4-piperidinylpropyl	methyl	benzyloxycarbonyl	OH	
2149	4-piperidinylpropyl	methyl	benzyloxycarbonyl	OMe	
2150	4-piperidinylpropyl	methyl	n-butyloxycarbonyl	OH	
2151	4-piperidinylpropyl	methyl	n-butyloxycarbonyl	OMe	
2152	4-amidinopiperidinyl	methyl	n-butylsulfonyl	OH	
2153	4-amidinopiperidinyl	methyl	n-butylsulfonyl	OMe	
2154	4-amidinopiperidinyl	methyl	2-methylphenylsulfonyl	OH	
2155	4-amidinopiperidinyl	methyl	2-bromophenylsulfonyl	OH	
2156	4-amidinopiperidinyl	methyl	3-methylphenylsulfonyl	OH	
2157	4-amidinopiperidinyl	methyl	3-methylphenylsulfonyl	OMe	
2158	4-amidinopiperidinyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OH	
2159	4-amidinopiperidinyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OMe	
2160	4-amidinopiperidinyl	methyl	styrylsulfonyl	OH	
2161	4-amidinopiperidinyl	methyl	benzyloxycarbonyl	OH	
2162	4-amidinopiperidinyl	methyl	benzyloxycarbonyl	OMe	
2163	4-amidinopiperidinyl	methyl	n-butyloxycarbonyl	OH	
2164	4-amidinopiperidinyl	methyl	n-butyloxycarbonyl	OMe	

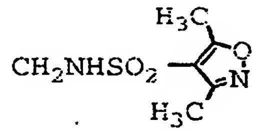
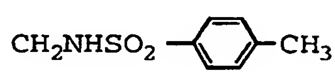
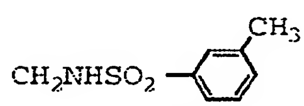
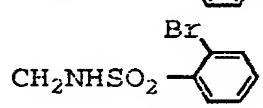
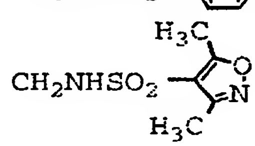
2165	4-amidinopiperidinyl-methyl	methyl	n-butylsulfonyl	OH
2166	4-amidinopiperidinyl-methyl	methyl	n-butylsulfonyl	OMe
2167	4-amidinopiperidinyl-methyl	methyl	2-methylphenylsulfonyl	OH
2168	4-amidinopiperidinyl-methyl	methyl	2-bromophenylsulfonyl	OH
2169	4-amidinopiperidinyl-methyl	methyl	3-methylphenylsulfonyl	OH
2170	4-amidinopiperidinyl-methyl	methyl	3-methylphenylsulfonyl	OMe
2171	4-amidinopiperidinyl-methyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OH
2172	4-amidinopiperidinyl-methyl	methyl	3,5-dimethylisoxazolyl sulfonyl	OMe
2173	4-amidinopiperidinyl-methyl	methyl	styrylsulfonyl	OH
2174	4-amidinopiperidinyl-methyl	methyl	benzyloxycarbonyl	OH
2175	4-amidinopiperidinyl-methyl	methyl	benzyloxycarbonyl	OMe
2176	4-amidinopiperidinyl-methyl	methyl	n-butyloxycarbonyl	OH
2177	4-amidinopiperidinyl-methyl	methyl	n-butyloxycarbonyl	OMe
2178	4-amidinophenyl	methyl	phenylcarbonyl	OMe
2179	4-amidinophenyl	methyl	phenylcarbonyl	OH
2180	4-amidinophenyl	methyl	2,6-methylphenylcarbonyl	OMe
2181	4-amidinophenyl	methyl	2,6-methylphenylcarbonyl	OH
2182	4-amidinophenyl	methyl	2-methylphenylcarbonyl	OMe
2183	4-amidinophenyl	methyl	2-methylphenylcarbonyl	OH
2184	4-amidinophenyl	methyl	2-bromophenylcarbonyl	OMe
2185	4-amidinophenyl	methyl	2-bromophenylcarbonyl	OH
2186	4-amidinophenyl	methyl	3-methylphenylcarbonyl	OMe
2187	4-amidinophenyl	methyl	3-methylphenylcarbonyl	OH
2188	4-amidinophenyl	methyl	3,5-dimethyl-isoxazoylcarbonyl	OMe
2189	4-amidinophenyl	methyl	3,5-dimethyl-isoxazoylcarbonyl	OH
2190	4-piperidinylethyl	methyl	phenylcarbonyl	OMe
2191	4-piperidinylethyl	methyl	phenylcarbonyl	OH
2192	4-piperidinylethyl	methyl	2,6-methylphenylcarbonyl	OMe
2193	4-piperidinylethyl	methyl	2,6-methylphenylcarbonyl	OH
2194	4-piperidinylethyl	methyl	2-methylphenylcarbonyl	OMe
2195	4-piperidinylethyl	methyl	2-methylphenylcarbonyl	OH
2196	4-piperidinylethyl	methyl	2-bromophenylcarbonyl	OMe
2197	4-piperidinylethyl	methyl	2-bromophenylcarbonyl	OH
2198	4-piperidinylethyl	methyl	3-methylphenylcarbonyl	OMe
2199	4-piperidinylethyl	methyl	3-methylphenylcarbonyl	OH
2200	4-piperidinylethyl	methyl	3,5-dimethyl-isoxazoylcarbonyl	OMe
2201	4-piperidinylethyl	methyl	3,5-dimethyl-isoxazoylcarbonyl	OH
2202	4-piperidinylethyl	methyl	n-butyloxycarbonyl	OH

Table 11.



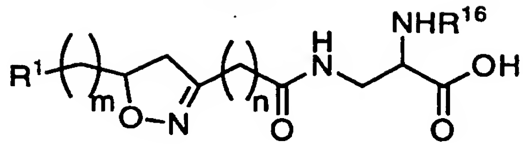
(VI)

Example Number	R^2	R^8	Y	MS $(M+H)^+$
2220	H	$CH_2NHCO_2n\text{-}C_3H_7$	OH	
2221	H	$CH_2NHCO_2n\text{-}C_4H_9$	OH	
2222	H	$CH_2NHCO_2n\text{-}C_5H_{11}$	OH	
2223	H	$CH_2NHCO_2CH_2Ph$	OH	
2224	H	$CH_2NHCO_2CH_2CH_2Ph$	OH	
2225	H	$CH_2NHCO_2i\text{-}C_4H_9$	OH	
2226	H	$CH_2NHSO_2CH_2Ph$	OH	
2227	H		OH	
2228	H		OH	
2229	H		OH	
2230	H		OH	
2231	n-Bu	$CH_2NHCO_2n\text{-}C_3H_7$	OH	
2232	n-Bu	$CH_2NHCO_2n\text{-}C_4H_9$	OH	
2233	n-Bu	$CH_2NHCO_2n\text{-}C_5H_{11}$	OH	
2234	n-Bu	$CH_2NHCO_2CH_2Ph$	OH	
2235	n-Bu	$CH_2NHCO_2CH_2CH_2Ph$	OH	
2236	n-Bu	$CH_2NHCO_2i\text{-}C_4H_9$	OH	
2237	n-Bu	$CH_2NHSO_2CH_2Ph$	OH	
2238	n-Bu		OH	
2239	n-Bu		OH	
2240	n-Bu		OH	

2241	*n*-Bu		OH
2242	o-methoxy-benzyl	$-CH_2CH_3$	OH
2243	o-methoxy-benzyl	$-CH=CH_2$	OH
2244	o-methoxy-benzyl	$-C\equiv CH$	OH
2245	o-methoxy-benzyl	CH_2NHCO_2*n*-C_3H_7	OH
2246	o-methoxy-benzyl	CH_2NHCO_2*n*-C_4H_9	OH
2247	o-methoxy-benzyl	CH_2NHCO_2*n*-C_5H_{11}	OH
2248	o-methoxy-benzyl	$CH_2NHCO_2CH_2Ph$	OH
2249	o-methoxy-benzyl	$CH_2NHCO_2CH_2CH_2Ph$	OH
2250	o-methoxy-benzyl	CH_2NHCO_2*i*-C_4H_9	OH
2251	o-methoxy-benzyl	$CH_2NHSO_2CH_2Ph$	OH
2252	o-methoxy-benzyl		OH
2253	o-methoxy-benzyl		OH
2254	o-methoxy-benzyl		OH
2255	o-methoxy-benzyl		OH
2256	o-methoxy-benzyl	$-CH_2CH_3$	OH
2257	o-methoxy-benzyl	$-CH=CH_2$	OH

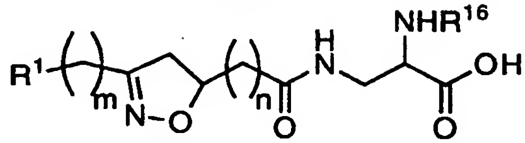
2258	o-methoxy-benzyl	-C∫CH	OH

Table 12



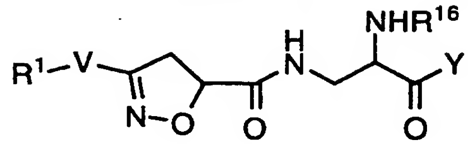
Ex No.	R^1	R^{16}	m	n	MS $(M+H)^+$
2280	guanidino	benzyloxycarbonyl	2	2	449
2281	guanidino	benzyloxycarbonyl	1	2	435
2282	guanidino	benzyloxycarbonyl			
2283	guanidino	benzyloxycarbonyl			
2284	guanidino	benzyloxycarbonyl			
2285	guanidino	benzyloxycarbonyl			

Table 13



Ex No.	R^1	R^{16}	m	n	MS $(M+H)^+$
2400	guanidino	benzyloxycarbonyl	2	2	449
2401	guanidino	benzyloxycarbonyl	3	0	435
2402	guanidino	benzyloxycarbonyl	5	0	463
2403	guanidino	benzyloxycarbonyl	3	2	463
2404	guanidino	benzyloxycarbonyl	4	2	477
2405	guanidino	benzyloxycarbonyl	2	0	421
2406	guanidino	benzyloxycarbonyl	4	0	449

Table 14



Ex No.	R^1–V	R^{16}	Y	MS $(M+H)^+$
2420	4-piperidinylpropyl	n-butyloxycarbonyl	OMe	441
2421	4-piperidinylpropyl	4-methylphenylsulfonyl	OMe	495
2422	4-piperidinylpropyl	4-methylphenylsulfonyl	OH	481
2423	4-piperidinylpropyl	n-butyloxycarbonyl	OH	427

Utility

The compounds of this invention possess antiplatelet efficacy, as evidenced by their activity in standard platelet aggregation assays or platelet fibrinogen binding assays, as described below. A compound is considered to be active in these assays if it has an IC_{50} value of less than about 1 m*M*. Platelet aggregation and fibrinogen binding assays which may be used to demonstrate the antiplatelet activity of the compounds of the invention are described below.

Platelet Aggregation Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin-free for at least two weeks prior to blood collection. Blood was collected into 10 mL citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 150 x g at room temperature, and platelet-rich plasma (PRP) was removed. The remaining blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet-poor plasma (PPP) was removed. Samples were assayed on a aggregometer (PAP-4 Platelet Aggregation Profiler), using PPP as the blank (100% transmittance). 200 µL of PRP was added to each micro test tube, and transmittance was set to 0%. 20 µL of various agonists (ADP, collagen, arachidonate, epinephrine, thrombin) were added to each tube, and the aggregation profiles were plotted (% transmittance versus time). The results are expressed as % inhibition of agonist-induced platelet aggregation. For the IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

Ester prodrugs were preincubated (10^{-3} M F.C.) with 100 IU/mL Porcine liver esterase (Sigma Chemical Co., St. Louis, MO, #E-3128) for 2 hours at 37 °C. Aliquots are then diluted in 0.1 M Tris, pH 7.4, to the desired concentrations. Aliquots of 20 µl of the esterase pretreated prodrugs are added to 200 µl of human platelet

rich plasma. Samples were placed in platelet profiler (aggregometer) for 8 minutes at 37 °C, followed by the addition of 100 μM Adenosine Diphosphate, (Sigma Chemical Co., St. Louis, MO, #A-6521), to induce platelet aggregation. Platelet aggregation was allowed to proceed for 5 minutes. Percent inhibition is calculated using percent aggregation in the presence of the test compound divided by percent aggregation of control, times 100. This value is subtracted from 100, yielding percent inhibition. Calculation of IC_{50} is performed on a Texas Instruments TI59 with an IC_{50} program.

Purified GPIIb/IIIa-Fibrinogen Binding ELISA

The following reagents are used in the GPIIb/IIIa-fibrinogen binding ELISA:

purified GPIIb/IIIa (148.8 μg/mL);
biotinylated fibrinogen (~ 1 mg/mL or 3000 nM);
anti-biotin alkaline phosphatase conjugate (Sigma no. A7418);
flat-bottom, high binding, 96-well plates (Costar Cat. no. 3590);
phosphatase substrate (Sigma 104) (40 mg capsules);
bovine serum albumin (BSA) (Sigma no. A3294);
Alkaline Phosphatase buffer - 0.1 M glycine-HCl, 1 mM $MgCl_2 \bullet 6H_2O$, 1 mM $ZnCl_2$, pH 10.4;
Binding buffer - 20 mM Tris-HCl, 150 mM NaCl, 1 mM $CaCl_2.2H_2O$, 0.02% NaN_3, pH 7.0;
Buffer A - 50 mM Tris-HCl, 100 mM NaCl, 2 mM $CaCl_2.2H_2O$, 0.02% NaN_3, pH 7.4;
Buffer A + 3.5% BSA (Blocking buffer);
Buffer A + 0.1% BSA (Dilution buffer);
2N NaOH.

The following method steps are used in the GPIIb/IIIa-fibrinogen binding ELISA:

Coat plates with GPIIb/IIIa in Binding buffer (125 ng/100 µL/well) overnight at 4 °C (Leave first column uncoated for non-specific binding). Cover and freeze plates at -70 °C until used. Thaw plate 1 hour at room temperature or overnight at 4 °C. Discard coating solution and wash once with 200 µL Binding buffer per well. Block plate 2 hours at room temperature on shaker with 200 µL Buffer A + 3.5% BSA (Blocking buffer) per well. Discard Blocking buffer and wash once with 200 µL Buffer A + 0.1% BSA (Dilution buffer) per well. Pipet 11 µL of test compound (10X the concentration to be tested in Dilution buffer) into duplicate wells. Pipet 11 µL Dilution buffer into non-specific and total binding wells. Add 100 µL Biotinylated fibrinogen (1/133 in Dilution buffer, final concentration = 20 nM) to each well. Incubate plates for 3 hours at room temperature on a plate shaker. Discard assay solution and wash twice with 300 µL Binding buffer per well. Add 100 µL Anti-biotin alkaline phosphatase conjugate (1/1500 in Dilution buffer) to each well. Incubate plates for 1 hour at room temperature on plate shaker. Discard conjugate and wash twice with 300 51 Binding buffer per well. Add 100 µL Phosphatase substrate (1.5 mg/mL in Alkaline phosphatase buffer) to each well. Incubate plate at room temperature on shaker until color develops. Stop color development by adding 25 µL 2N NaOH per well. Read plate at 405 nm. Blank against non-specific binding (NSB) well. % Inhibition is calculated as

100 - (Test Compound Abs/Total Abs)x100.

<u>Platelet-Fibrinogen Binding Assay:</u> Binding of ^{125}I-fibrinogen to platelets was performed as described by Bennett et al. (1983) Proc. Natl. Acad. Sci. USA 80: 2417-2422, with some modifications as described below. Human PRP (h-PRP) was applied to a Sepharose column for the purification of platelet fractions. Aliquots of platelets (5 X 10^8 cells) along with 1 m*M* calcium chloride were

added to removable 96 well plates prior to the activation of the human gel purified platelets (h-GPP). Activation of the human gel purified platelets was achieved using ADP, collagen, arachidonate, epinephrine, and/or thrombin in the presence of the ligand, ^{125}I-fibrinogen. The ^{125}I-fibrinogen bound to the activated platelets was separated from the free form by centrifugation and then counted on a gamma counter. For an IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

The compounds of Formula I of the present invention may also possess thrombolytic efficacy, that is, they are capable of lysing (breaking up) already formed platelet-rich fibrin blood clots, and thus are useful in treating a thrombus formation, as evidenced by their activity in the tests described below. Preferred compounds of the present invention for use in thrombolysis include those compounds having an IC_{50} value (that is, the molar concentration of the compound capable of achieving 50% clot lysis) of less than about 1 μM, more preferably an IC_{50} value of less than about 0.1 μM.

Thrombolytic Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin free for at least two weeks prior to blood collection, and placed into 10 ml citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet rich plasma (PRP) was removed. To the PRP was then added 1×10^{-3} M of the agonist ADP, epinephrine, collagen, arachidonate, serotonin or thrombin, or a mixture thereof, and the PRP incubated for 30 minutes. The PRP was centrifuged for 12 minutes at 2500 x g at room temperature. The supernatant was then poured off, and the platelets remaining in the test tube were resuspended in platelet poor plasma (PPP), which served as a plasminogen source. The suspension was then assayed on a Coulter Counter (Coulter Electronics, Inc., Hialeah, FL), to determine the platelet count at the

zero time point. After obtaining the zero time point, test compounds were added at various concentrations. Test samples were taken at various time points and the platelets were counted using the Coulter Counter. To determine the percent of lysis, the platelet count at a time point subsequent to the addition of the test compound was subtracted from the platelet count at the zero time point, and the resulting number divided by the platelet count at the zero time point. Multiplying this result by 100 yielded the percentage of clot lysis achieved by the test compound. For the IC_{50} evaluation, the test compounds were added at various concentrations, and the percentage of lysis caused by the test compounds was calculated.

The compounds of Formula I of the present invention are also useful for administration in combination with anti-coagulant agents such as warfarin or heparin, or antiplatelet agents such as aspirin, piroxicam or ticlopidine, or thrombin inhibitors such as boropeptides, hirudin or argatroban, or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof.

The compounds of Formula I of the present invention may also be useful as antagonists of other integrins such as for example, the α_v/β_3 or vitronectin receptor, α_4/β_1 or α_5/β_1 and as such may also have utility in the treatment and diagnosis of osteoporosis, cancer metastasis, diabetic retinopathy, rheumatoid arthritis, inflammation, and autoimmune disorders. The compounds of Formula I of the present invention may be useful for the treatment or prevention of other diseases which involve cell adhesion processes, including, but not limited to, infammation, bone degradation, rheumatoid arthritis, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplantation, septic shock, psoriasis, eczema, contact dermatitis, osteoporosis, osteoarthritis, atherosclerosis, metastasis, wound healing, diabetic

timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent. Finally, the compounds of the invention may also be administered intranasally.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, glycoprotein IIb/IIIa (GPIIb/IIIa), in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents, such as a second antiplatelet agent such as aspirin or ticlopidine which are agonist-specific. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient,and the effect desired. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form *via* topical use of suitable intranasal vehicles, or *via* transdermal routes, using those forms of transdermal skin patches wall known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

It has unexpectedly been found that compounds of the present invention can be delivered by the nasal route of administration. The delivery of Example 327 (and it's free acid Example 300) through the nasal route provided very high bioactivity (inhibition of platelet aggregation) that was similar to that observed after administering the same dose intravenously. Also dog to dog variability was very small. For example, nasal and i.v. administration of 0.025 mg/kg gave similar profiles of platelet aggregation inhibition, however comparable effect after oral administration was only seen at doses equal or greater than 0.4 mg/kg. Therefore, the advantages of delivering Example 327 nasally are to enhance bioavailability and reduce variability. The latter is very important due to the steep dose response of these types of compounds.

The active ingredient can be administered intranasally to a mammal at a dosage range of about 0.01

to 0.5 mg/kg while the preferred dosage range is about 0.01-0.1 mg/kg.

Compositions of the active ingredients can be administered intranasally by preparing a suitable formulation of the active ingredient by procedures well known to those skilled in the art. Preferably the formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. These ingredients are known to those skilled in the preparation of nasal dosage forms and some of these can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, 17th edition, 1985, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters, emulsifiers or dispersing agents, preservatives, surfactants, jelling agents, or buffering and other stabilizing and solubilizing agents may also be present. Preferably, the nasal dosage form should be isotonic with nasal secretions.

An example of a nasal solution composition of this invention includes:

Active Drug	0.2-2 g
Sorbitol	0.6 g
Benzalkonium chloride	0.002 g
Hydrochloric acid	to adjust pH
Sodium hydroxide	to adjust pH
Purified water	to 10 mL

In this example the active drug can be in one vial and the rest of the formulation can be in another vial. The drug can be reconstituted when needed.

The formulation of this invention may be varied to include: (1) other acids and bases to adjust the pH; (2) other tonicity imparting agents such as glycerin and dextrose; (3) other antimicrobial preservatives such as other parahydroxy benzoic acid esters, sorbate, benzoate, propionate, chlorbutanol, phenylethyl alcohol, and mercurials; (4) other viscosity imparting agents such as sodium carboxy-methylcellulose microcrystalline cellulose, polyvinyl-pyrrolidone, polyvinyl alcohol and other gums; (5) suitable absorption enhancers; (6) stabilizing agents such as antioxidants, like bisulfite and ascorbate, metal chelating agents such as sodium edetate and drug solubility enhancers such as polyethylene glycols.

The above formulation can be administered as drops, sprays, aerosols or by any other intranasal dosage form. Optionally, the delivery system can be a unit dose delivery system. The volume of solution or suspension delivered per dose can be anywhere from 5 to 400 µL, and preferably between 50 and 150 µL. Delivery systems for these various dosage forms can be dropper bottles, plastic squeeze units, atomizers, nebulizers or pharmaceutical aerosols in either unit dose or multiple dose packages.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol

and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamallar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral

solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 1-20 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 1-20 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 1-20 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension is prepared for oral administration so that each 5 mL contain 1-20 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

The compounds of the present invention may be administered in combination with a second therapeutic agent selected from: an anti-coagulant agent such as warfarin or heparin; an anti-platelet agent such as aspirin, piroxicam or ticlopidine; a thrombin inhibitor such as a boropeptide thrombin inhibitor, or hirudin; or a thrombolytic agent such as plasminogen activators, such as tissue plasminogen activator, anistreplase, urokinase or streptokinase. The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent) may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent). When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart.

A preferable route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent (anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent) are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Although the proper dosage of the compound of Formula I when administered in combination with the second therapeutic agent will be readily ascertainable by a medical practitioner skilled in the art, once armed with the present disclosure, by way of general guidance, where the compounds of this invention are combined with anti-coagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the novel compounds of this invention generally may be present in an amount of about 1 to 10 milligrams per dosage unit, and the anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with a second anti-platelet agent, by way of general guidance, typically a daily dosage may be about

0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the additional anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of anti-platelet agents, per kilogram of patient body weight.

Further, by way of general guidance, where the compounds of Formula-I are adminstered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a

sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the inhibition of platelet aggregation, the treatment of blood clots, and/or the treatment of thromboembolic disorders, which comprise one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for

administration, and/or guidelines for mixing the components, may also be included in the kit.

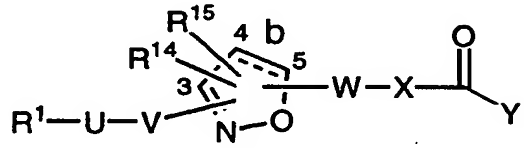
In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

PATENT APPLICATION
DM-6685-B

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:

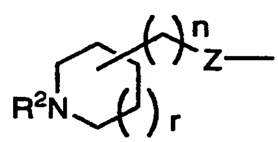


(I)

or pharmaceutically acceptable salt form thereof wherein:

b is a carbon-carbon single or double bond;

R^1 is selected from $R^2(R^3)N(CH_2)_qZ$-, $R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ$-, piperazinyl-$(CH_2)_qZ$- or



;

Z is selected from O, S, S(=O), or $S(=O)_2$;

R^2 and R^3 are independently selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_6-C_{10} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_6-C_{10} aryloxycarbonyl, aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl;

U is selected from:

a single bond,

-(C_1-C_7 alkyl)-,

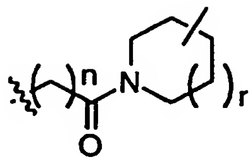
-(C_2-C_7 alkenyl)-,

-(C_2-C_7 alkynyl)-,
-(aryl)- substituted with 0-3 R^{6a}, or
-(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:
a single bond;
-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;
-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;
-(C_2-C_7 alkynyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;
-(aryl)-, substituted with 0-2 groups independently selected from R^6 or R^7;
-(pyridyl)-, substituted with 0-2 groups independently selected from R^6 or R^7; or
-(pyridazinyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

W is selected from:
a single bond,
-(C_1-C_7 alkyl)-,
-(C_2-C_7 alkenyl)-,
-(C_2-C_7 alkynyl)-, or
-$(C(R^5)_2)_nC(=O)N(R^{5a})$-;

X is selected from:
a single bond;
-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^4, R^8 or R^{14};
-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^4, R^8 or R^{14};
-(C_2-C_7 alkynyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14}; or


;

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy; or $(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

R^4 and R^{4b} are independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^5 is selected from H, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} can be taken together to be 3-azabicyclononyl, 1-piperidinyl, 1-morpholinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^{5a}$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or

fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^{5a}$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to C_{11} arylalkyl;

R^8 is selected from:

H;

R^6;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6;

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

C_5-C_6 cycloalkenyl, substituted with 0-2 R^6;

aryl, substituted with 0-2 R^6;

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10}

alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylsulfonyl, heteroarylalkylcarbonyl or aryl(C_1-C_{10} alkoxy)carbonyl;

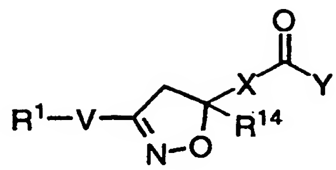
R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{15} is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_1-C_{10} alkoxy, substituted with 0-6 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;
C_1-C_{10} alkoxycarbonyl substituted with 0-8 R^6;
CO_2R^5; or
$-C(=O)N(R^5)R^{5a}$;

provided that when b is a double bond, only one of R^{14} or R^{15} is present;

n is 0-4;
q is 2-7;
r is 0-3;
provided that n, q, and r are chosen such that the number of in-chain atoms between R^1 and Y is in the range of 8-18.

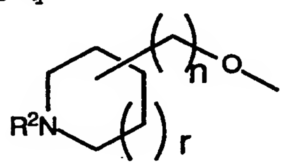
2. A compound of Claim 1 of Formula II:



(II)

wherein:

R^1 is selected from $R^2HN(CH_2)_qO$-, $R^2HN(R^2N{=})CNH(CH_2)_qO$-, piperazinyl-$(CH_2)_qO$-, or



;

R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_{10} alkoxycarbonyl;

R^8 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated;

R^6 and R^7 are selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo.

3. A compound of Claim 2 wherein:

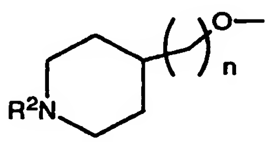
X is selected from:
- a single bond;
- $-(C_1$-C_7 alkyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14};
- $-(C_2$-C_7 alkenyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14};

-(C_2-C_7 alkynyl)-, substituted with 0-2 groups independently selected from R^4, R^8 or R^{14};

R^8 is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated.

4. A compound of Claim 2 wherein:

R^1 is



;

V is phenylene or pyridylene;

n is 1 or 2;

X is -(C_1-C_2)alkyl- substituted with 0-2 R^4

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;

1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^4 is $-NR^{12}R^{13}$;

R^{12} is H, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylsulfonyl, arylalkylsulfonyl, heteroarylsulfonyl, arylsulfonyl, benzyl, benzoyl, phenoxycarbonyl, benzyloxycarbonyl, arylalkylsulfonyl, pyridylcarbonyl, or pyridylmethylcarbonyl;

R^{13} is H.

5. A compound of Claim 1, or a pharmaceutically acceptable salt form thereof, selected from:

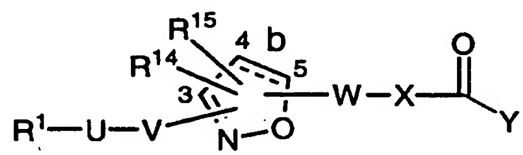
5(*R,S*)-3-[[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl]acetic acid;
5(*R,S*)-*N*-(butanesulfonyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;
5(*R,S*)-*N*-(α-toluenesulfonyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;
5(*R,S*)-*N*-[(benzyloxy)carbonyl]-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;
5(*R,S*)-*N*-(pentanoyl)-L-{3-[4-(2-piperidin-4-yl)ethoxyphenyl]isoxazolin-5-yl}glycine;
5(*R,S*)-3-{[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;
2(*R,S*)-5(*R,S*)-*N*-(butanesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2(*R,S*)-5(*R,S*)-*N*-(α-toluenesulfonyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2(*R,S*)-5(*R,S*)-*N*-[(benzyloxy)carbonyl]amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid;

2(*R,S*)-5(*R,S*)-*N*-(pentanoyl)amino-{3-[4-(piperidin-4-yl)methoxyphenyl]isoxazolin-5-yl}propanoic acid.

6. A compound of Formula I:

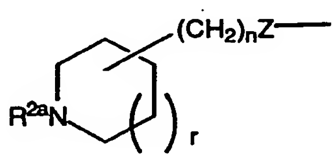


(I)

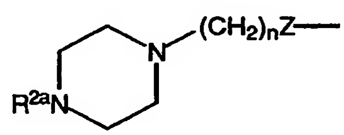
or a pharmaceutically acceptable salt form thereof wherein:

b is a carbon-carbon single or double bond;

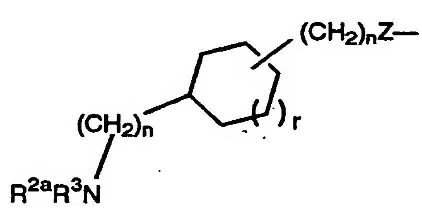
R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N=)C-$, $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, $R^2(R^3)N(R^5ON=)C-$;



,



or



;

Z is selected from: a bond, O, S, S(=O), $S(=O)_2$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11}

cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3,

$S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

R^{2a} is R^2 or $R^2(R^3)N(R^2N{=})C-$;

U is selected from:
- a single bond,
- $-(C_1$-C_7 alkyl$)-$,
- $-(C_2$-C_7 alkenyl$)-$,
- $-(C_2$-C_7 alkynyl$)-$,
- -(aryl)- substituted with 0-3 R^{6a}, or
- -(pyridyl)- substituted with 0-3 R^{6a};

V is selected from:
- a single bond;
- $-(C_1$-C_7 alkyl$)-$, substituted with 0-3 groups independently selected from R^6 or R^7;
- $-(C_2$-C_7 alkenyl$)-$, substituted with 0-3 groups independently selected from R^6 or R^7;
- $-(C_2$-C_7 alkynyl$)-$, substituted with 0-3 groups independently selected from R^6 or R^7;
- -(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^6 or R^7;
- -(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^6 or R^7; or
- -(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^6 or R^7,

Q is selected from
a single bond,
$-O-$, $-S(O)_m-$, $-N(R^{12})-$, $-(CH_2)_m-$, $-C(=O)-$, $-N(R^{5a})C(=O)-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $-OCH_2-$, $-CH_2N(R^{12})-$, $-N(R^{12})CH_2-$, $-CH_2C(=O)-$, $-C(=O)CH_2-$, $-CH_2S(O)_m-$, or $-S(O)_mCH_2-$,

provided that when b is a single bond, and R^1-U-V- is a substituent on C5 of the central 5-membered ring of Formula I, then Q is not $-O-$, $-S(O)_m-$, $-N(R^{12})-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $CH_2N(R^{12})-$ or $-CH_2S(O)_m-$;

W is selected from:

$-(C(R^4)_2)_nC(=O)N(R^{5a})-$, or
$-C(=O)-N(R^{5a})-(C(R^4)_2)_n-$;

X is selected from:
a single bond,
$-(C(R^4)_2)_n-C(R^4)(R^8)-C(R^4)(R^{4a})-$, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl;

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, $(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

alternately, two R^4 groups on adjacent carbon atoms may join to form a bond thereby to form a carbon-carbon double or triple bond between such adjacent carbon atoms;

R^{4a} is selected from H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$,
C_1-C_{10} alkyl substituted with 0-3 R^6,
aryl substituted with 0-3 R^6, or
C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_7-C_{14} bicycloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6

alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, -N(R^{12})R^{13}; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

R^5 is selected from H, C_1-C_8 alkyl, C_3-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3-C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} when both are substituents on the same nitrogen atom (as in -NR^5R^{5a}) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, -N(R^{12})R^{13}, cyano, halo, CF_3, CHO, CO_2R^5, C(=O)R^{5a}, CONR^5R^{5a}, OC(=O)R^{5a}, OC(=O)OR^{5b}, OR^{5a}, OC(=O)NR^5R^{5a}, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, NR^{5a}C(=O)R^{5a}, NR^{5a}C(=O)OR^{5b}, NR^{5a}C(=O)NR^5R^{5a}, N$R^{5a}SO_2NR^5R^{5a}$, N$R^{5a}SO_2R^5$, S(O)$_pR^{5a}$,

$SO_2NR^5R^{5a}$, $SiMe_3$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^{5a}$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to C_{11} arylalkyl;

R^8 is selected from:
R^6;
C_1-C_{10} alkyl, substituted with 0-3 R^6;
C_2-C_{10} alkenyl, substituted with 0-3 R^6;
C_2-C_{10} alkynyl, substituted with 0-3 R^6;
C_3-C_8 cycloalkyl, substituted with 0-3 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-3 R^6;
aryl, substituted with 0-3 R^6;

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl(C_2-C_{10} alkenyl)sulfonyl, heteroarylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_7-C_{11} arylcarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylsulfonyl, heteroarylalkylcarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryl groups are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{15} is selected from:

H; R^6; $-CO_2R^5$; $-C(=O)N(R^5)R^{5a}$;

C_1-C_{10} alkoxycarbonyl substituted with 0-2 R^6;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_1-C_{10} alkoxy, substituted with 0-3 R^6;

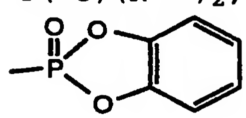
aryl, substituted with 0-3 R^6; or

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

provided that when b is a double bond, only one of R^{14} or R^{15} is present;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,
$-C(=O)-R^{18b}$,
$-C(=O)N(R^{18b})_2$,
$-C(=O)NHSO_2R^{18a}$,
$-C(=O)NHC(=O)R^{18b}$,
$-C(=O)NHC(=O)OR^{18a}$,
$-C(=O)NHSO_2NHR^{18b}$,
$-C(=S)-NH-R^{18b}$,
$-NH-C(=O)-O-R^{18a}$,
$-NH-C(=O)-R^{18b}$,
$-NH-C(=O)-NH-R^{18b}$,
$-SO_2-O-R^{18a}$,
$-SO_2-R^{18a}$,
$-SO_2-N(18^b)_2$,
$-SO_2-NHC(=O)O18^b$,
$-P(=S)(OR^{18a})_2$,
$-P(=O)(OR^{18a})_2$,
$-P(=S)(R^{18a})_2$,
$-P(=O)(R^{18a})_2$, or

 ;

R^{17} is selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-;

R^{18a} is selected from:
C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N,

said heterocyclic ring being substituted with 0-4 R^{19},

C_1-C_6 alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

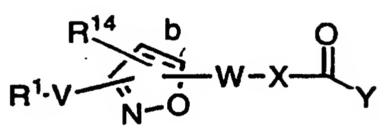
n is 0-4;

q is 1-7;

r is 0-3;

provided that n, q and r are chosen such that the number of in-chain atoms connecting R^1 and Y is in the range of 8-18.

7. A compound of Claim 6 of Formula Ia:



(Ia)

wherein:

Z is selected from a bond, O, or S;

R^2 is selected from H, aryl(C_1-C_{10} alkoxy)carbonyl, or C_1-C_{10} alkoxycarbonyl;

W is $-(CH_2)_nC(=O)N(R^{5a})-$;

X is $-(C(R^4)_2)_n-C(R^4)(R^8)-CH(R^4)-$, with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, $-NR^5R^{5a}$, CO_2R^5, $S(O)_mR^5$, OR^5, cyano, halo;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a 5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^7 is selected from selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^8 is selected from:

$-CONR^5NR^{5a}$; $-CO_2R^5$;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6,

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

C_5-C_6 cycloalkenyl, substituted with 0-3 R^6;

aryl, substituted with 0-2 R^6;

5-10 membered heterocyclic ring containing 1-3 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylcarbonyl, heteroarylsulfonyl, or heteroarylalkylcarbonyl, wherein said aryl groups are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2.

8. A compound of Claim 7 wherein:

Z is selected from a bond or O;

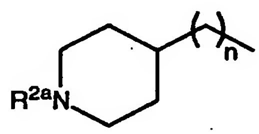
W is $-(CH_2)_nC(=O)N(R^{12})-$;

X is $-C(R^4)(R^8)-C(R^4)_2-$.

9. A compound of Claim 7 wherein:

R^1 is $R^2NHC(=NR^2)-$ or $R^2NHC(=NR^2)NH-$ and V is phenylene or pyridylene, or

R^1 is



and V is a single bond;

n is 1 or 2;

X is $-CHR^8CH_2-$;

Y is selected from:

hydroxy;

C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-;

ethylcarbonyloxymethoxy-;

t-butylcarbonyloxymethoxy-;

cyclohexylcarbonyloxymethoxy-;

1-(methylcarbonyloxy)ethoxy-;

1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;

1-(cyclohexylcarbonyloxy)ethoxy-;

i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^6 is selected from H, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, $-NR^5R^{5a}$, CO_2R^5, $S(O)_mR^5$, OR^5, cyano, halo;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolyl, isoxazolinyl or morpholinyl;

R^8 is selected from:
$-CONR^5NR^{5a}$; $-CO_2R^5$;
C_1-C_{10} alkyl, substituted with 0-3 R^6;
C_2-C_{10} alkenyl, substituted with 0-3 R^6;
C_2-C_{10} alkynyl, substituted with 0-3 R^6,
C_3-C_8 cycloalkyl, substituted with 0-3 R^6;
aryl, substituted with 0-2 R^6;

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} is selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylsulfonyl, pyridylcarbonyl or pyridylmethylcarbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2; and

R^{13} is H.

10. A compound of Claim 6, or a pharmaceutically acceptable salt form thereof, selected from:

3(*R,S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-phenylpropanoic acid;

3(*R,S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-pentanoic acid;

3(*R*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}heptanoic acid;

3(*R,S*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylthio)butanoic acid;

3(*R,S*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(phenylsulfonamido)butanoic acid;

3(*R,S*)-{5(*R,S*)-*N*-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-4-(*n*-butylsulfonamido)butanoic acid;

3(*S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(adamantylmethylaminocarbonyl)propanoic acid;

3(*S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(1-azabicyclo[3.2.2]nonylcarbonyl)propanoic acid;

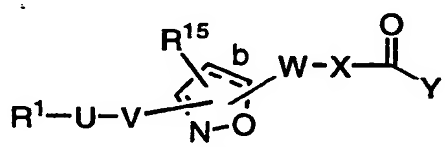
3(*S*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(phenethylaminocarbonyl)propanoic acid.

3(*R*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(3-pyridylethyl)propanoic acid.

3(*R*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(2-pyridylethyl)propanoic acid.

3(*R*)-{5(*R,S*)-N-[3-(4-amidinophenyl)isoxazolin-5-ylacetyl]amino}-3-(phenylpropyl)propanoic acid.

11. A compound of Claim 6 of Formula Ic:

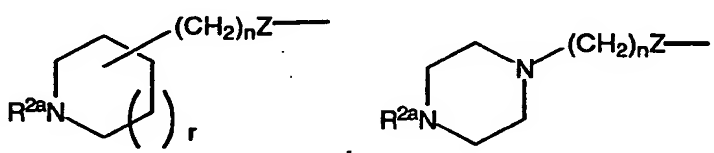


(Ic)

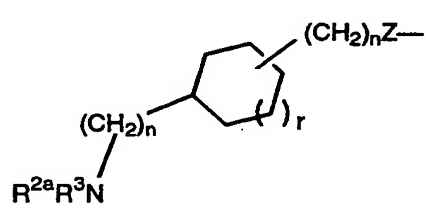
wherein:

b is a carbon-carbon single bond;

R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N=)C-$, $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, $R^2(R^3)N(R^5ON=)C-$;



, or



;

Z is selected from a bond, O, or S;

R^2 and R^3 are independently selected from: H; C_1-C_6 alkyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

R^{2a} is R^2 or $R^2(R^3)N(R^2N=)C$;

U is a single bond,

V is selected from:

a single bond;

-(C_1-C_7 alkyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkenyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(C_2-C_7 alkynyl)-, substituted with 0-3 groups independently selected from R^6 or R^7;

-(phenyl)-Q-, said phenyl substituted with 0-2 groups independently selected from R^6 or R^7;

-(pyridyl)-Q-, said pyridyl substituted with 0-2 groups independently selected from R^6 or R^7; or

-(pyridazinyl)-Q-, said pyridazinyl substituted with 0-2 groups independently selected from R^6 or R^7.

Q is selected from

a single bond,

-O-, $-S(O)_m-$, $-N(R^{12})-$, $-(CH_2)m-$, -C(=O)-, $-N(R^{5a})C(=O)-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $-OCH_2-$,

$-CH_2N(R^{12})-$, $-N(R^{12})CH_2-$, $-CH_2C(=O)-$, $-C(=O)CH_2-$, $-CH_2S(O)_m-$, or $-S(O)_mCH_2-$,

provided that when b is a single bond, and R^1-U-V- is a substituent on C5 of the central 5-membered ring of Formula Ic, then Q is not -O-, $-S(O)_m-$, $-N(R^{12})-$, $-C(=O)N(R^{5a})-$, $-CH_2O-$, $CH_2N(R^{12})-$ or $-CH_2S(O)_m-$;

W is selected from:
$-(C(R^4)_2)-C(=O)-N(R^{5a})-$, or
$-C(=O)-N(R^{5a})-(C(R^4)_2)-$;

X is $-C(R^4)_2-CHR^{4a}-$;

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{4a} is selected from hydroxy, C_1-C_{10} alkoxy, nitro, $-N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, or $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, or C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{12})R^{13}$, halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridyl;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, or adamantylmethyl, C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} can be taken together to be 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl,

thiazolidinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl or C_7-C_{11} arylalkoxycarbonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b}

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl, wherein said aryl groups being optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{15} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{16} is selected from:

-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-C(=O)N(R^{18b})$_2$,
-SO_2-R^{18a}, or
-SO_2-N(R^{18b})$_2$;

R^{17} is selected from: H or C_1-C_4 alkyl

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C2-C6 alkynyl, C_1-C_6 alkoxy,

C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, heteroaryl, aryl(C_1-C_6 alkyl)-, (C_1-C_4 alkly)sulfonyl, aryl-sulfonyl, or C_1-C_4 alkoxycarbonyl;

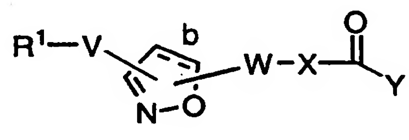
n is 0-4;

q is 1-7;

r is 0-3;

provided that n, q, and r are chosen such that the number of in-chain atoms between R^1 and Y is in the range of 8-17.

12. A compound of Claim 11 of Formula Ib:

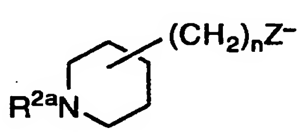


(Ib)

wherein:

b is a carbon-carbon single bond;

R^1 is selected from: $R^2(R^3)N$-, $R^2NH(R^2N=)C$-, $R^2NH(R^2N=)CNH$-, $R^2R^3N(CH_2)_{p'}Z$-, $R^2NH(R^2N=)CNH(CH_2)_{p''}Z$-, $R^2(R^3)NC(O)$-, $R^2(R^5O)N(R^2N=)C$-, $R^2(R^3)N(R^5ON=)C$-;



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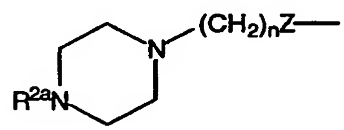
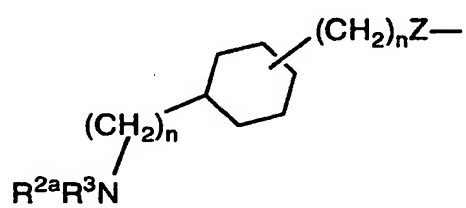


or



;

n is 0-1;

p' is 4-6;

p" is 2-4;

Z is selected from a bond or O;

V is a single bond, -(phenyl)- or -(pyridyl)-;

W is selected from:
$-(C(R^4)_2)-C(=O)-N(R^{5a})-$,
$-C(=O)-N(R^{5a})-CH_2-$;

X is selected from:
$-CH_2-CHN(R^{16})R^{17}-$, or
$-CH_2-CHNR^5R^{5a}-$;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{16} is selected from:
$-C(=O)-O-R^{18a}$,
$-C(=O)-R^{18b}$,
$-S(=O)_2-R^{18a}$ or
$-SO_2-N(R^{18b})_2$;

R^{17} is selected from H or C_1-C_5 alkyl;

R^{18a} is selected from:
C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},

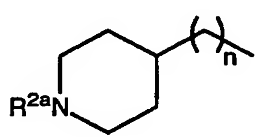
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19}.

13. A compound of Claim 11 wherein:

R^1 is $R^2NH(R^2N{=})C$- or $R^2HN(R^2N{=})CNH$- and V is phenylene or pyridylene, or
R^1 is



and V is a single bond;

n is 1 or 2;
R^{18a} is selected from:
C_1-C_4 alkyl substituted with 0-2 R^{19},
C_2-C_4 alkenyl substituted with 0-2 R^{19},

C_2-C_4 alkynyl substituted with 0-2 R^{19},
C_3-C_7 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_4 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_4 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, isoxazolinyl or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19}.

14. A compound of Claim 6, or pharmaceutically acceptable salt forms thereof, selected from:

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(phenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methyl-phenyl-sulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(butanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(propanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(ethanesulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(ethyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(1-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(1-(2-methyl)-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(2-methyl)-propyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(benzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methylbenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methoxybenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-chlorobenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-bromobenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-fluorobenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-phenoxybenzyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(methyloxyethyl)-oxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-pyridinylcarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-pyridinylcarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-pyridinyl-carbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(2-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(3-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-(4-pyridinyl)-acetyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-pyridyl-methyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-butyloxyphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-thienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R,S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(R)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-iodophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-2-methoxycarbonylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2,4,6-trimethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-trifluoromethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-fluorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-fluorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-methoxyphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2,3,5,6-tetramethylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-cyanophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-chlorophenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-propylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-phenylethylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-isopropylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-phenylpropylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-pyridylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(phenylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(benzylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(dimethylaminosulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(phenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(4-fluorophenylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(1-naphthylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(benzylaminocarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-bromo-2-thienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(3-methyl-2-benzothienylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(isobutyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5(*S*)-yl}-acetyl]-N2-(2-cyclopropylethoxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid;

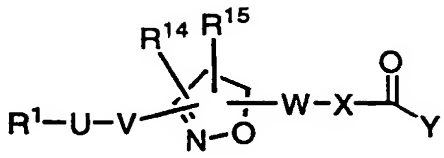
N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5(*R*)-yl}-acetyl]-N2-(3-methylphenylsulfonyl)-2,3-(S)-diaminopropanoic acid;

N^3-[2-{5-(4-formamidinophenyl)-isoxazolin-3(*R,S*)-yl}-acetyl]-N2-(n-butyloxycarbonyl)-2,3-(S)-diaminopropanoic acid.

15. A prodrug ester of a compound of Claim 14, said ester being selected from the group consisting of:

methyl;
ethyl;
isopropyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;
1-(ethylcarbonyloxy)ethyl-;
1-(t-butylcarbonyloxy)ethyl-;
1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxycarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
t-butyloxycarbonyloxymethyl-;
1-(i-propyloxycarbonyloxy)ethyl-;
1-(cyclohexyloxycarbonyloxy)ethyl-;
1-(t-butyloxycarbonyloxy)ethyl-;
dimethylaminoethyl-;
diethylaminoethyl-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;
1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

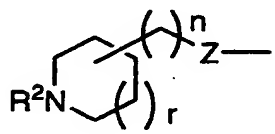
16. A compound of Formula Id:



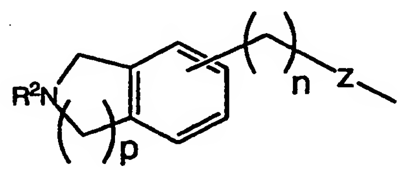
(Id)

or a pharmaceutically acceptable salt form thereof wherein:

R^1 is selected from is selected from $R^2(R^3)N$-, $R^2(R^3)N(R^2N{=})C$-, $R^2(R^3)N(R^2N{=})CN(R^2)$-, $R^2(R^3)N(CH_2)_qZ$-, $R^2(R^3)N(R^2N{=})C(CH_2)_qZ$-, $R^2(R^3)N(R^2N{=})CN(R^2)(CH_2)_qZ$-, piperazinyl-$(CH_2)_qZ$-, $R^2(R^3)NC(O)$-, $R^2(R^5O)N(R^2N{=})C$-, $R^2(R^3)N(R^5ON{=})C$-,



, or



;

Z is selected from a bond, O, S, S(=O), or S(=O)$_2$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, -$N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; , C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, -$N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, -$N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3

groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

U is selected from:
a single bond,
C_1-C_7 alkylene,
C_2-C_7 alkenylene,
C_2-C_7 alkynylene,
arylene substituted with 0-3 R^{6a},, or
pyridylene substituted with 0-3 R^{6a};

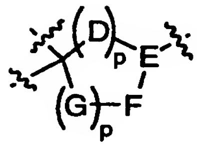
V is selected from:
a single bond;
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;

phenylene substituted with 0-4 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

X is selected from:
a single bond;
$-(CH_2)_nC(=O)N(R^{12})-$;
C_1-C_7 alkylene substituted with 0-6 R^4, R^8 or R^{15};
C_2-C_7 alkenylene substituted with 0-4 R^4, R^8 or R^{15};
C_2-C_7 alkynylene substituted with 0-4 R^4, R^8 or R^{15};

Y is selected from:
hydroxy,
C_1 to C_{10} alkyloxy,
C_3 to C_{11} cycloalkyloxy,
C_6 to C_{10} aryloxy,
C_7 to C_{11} aralkyloxy,
C_3 to C_{10} alkylcarbonyloxyalkyloxy,
C_3 to C_{10} alkoxycarbonyloxyalkyloxy,
C_2 to C_{10} alkoxycarbonylalkyloxy,
C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonylalkyloxy,
C_7 to C_{11} aryloxycarbonylalkyloxy,
C_8 to C_{12} aryloxycarbonyloxyalkyloxy,
C_8 to C_{12} arylcarbonyloxyalkyloxy,
C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy,
C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;
$(R^2)(R^3)N-(C_1-C_{10}$ alkoxy$)-$;

R^{14} and W are attached to the same carbon and taken together to form a spiro-fused, 5-7 membered ring structure of the formula:



;

D, E, F and G are each independently selected from:

$C(R^{6a})_2$;

carbonyl;

a heteroatom moiety selected from N, $N(R^{12})$, O, provided that no more than 2 of D, E, F and G are N, $N(R^{12})$, O, S, or C(=O);

alternatively, the bond between D and E, E and F, or F and G in such spiro-fused ring may be a carbon-nitrogen double bond or a carbon-carbon double bond;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^{5a}, $C(=O)R^{5a}$, $CONHR^{5a}$, $CON(R^{12})_2$, $OC(=O)R^{5a}$, $OC(=O)OR^{5a}$, OR^{5a}, $OC(=O)N(R^{12})_2$, $OCH_2CO_2R^{5a}$, $CO_2CH_2CO_2R^{5a}$, $N(R^{12})_2$, NO_2, $NR^{12}C(=O)R^{5a}$, $NR^{12}C(=O)OR^{5a}$, $NR^{12}C(=O)N(R^{12})_2$, $NR^{12}SO_2N(R^{12})_2$, $NR^{12}SO_2R^{5a}$, $S(O)_pR^{5a}$, $SO_2N(R^{12})_2$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^8 is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_2-C_{10} alkynyl, substituted with 0-6 R^6;
C_3-C_8 cycloalkyl, substituted with 0-6 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-5 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylsulfonyl, heteroarylalkylcarbonyl or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryl groups and heteroaryl groups are optionally substituted with 0-3 substituents selected from: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

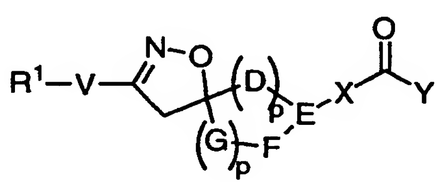
R^5 and R^{5a} are selected independently from H, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to

C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, C_7 to C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-8 R^4;

R^{15} is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_1-C_{10} alkoxy, substituted with 0-6 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;
C_1-C_{10} alkoxycarbonyl substituted with 0-8 R^6;
CO_2R^5; or
$-C(=O)N(R^{12})R^{13}$;

n is 0-4;
p is 1-3;
q is 1-7;
r is 0-3;
provided that n, p, q and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

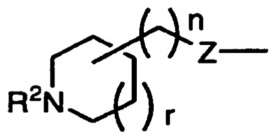
17. A compound of Claim 16 of Formula III:



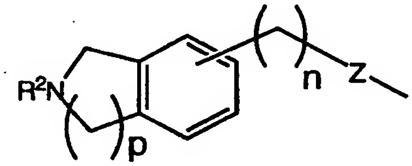
(III)

wherein:

R^1 is selected from R^2HN-, $H_2N(R^2N=)C-$, $H_2N(R^2N=)CNH-$, $R^2HN(CH_2)_qO-$, $H_2N(R^2N=)CNH(CH_2)_qO-$, piperazinyl-$(CH_2)_qO-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N=)C-$, $R^2(R^3)N(R^5ON=)C-$,



, or



;

R^2 and R^3 are selected from H; C_1-C_6 alkyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; heteroaryl(C_1-C_5)alkyl wherein the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or C_1-C_{10} alkoxycarbonyl;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

V is selected from:
a single bond;
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-3 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

X is selected from $-(CH_2)_nC(=O)N(R^{12})-$, C_1-C_7 alkylene substituted with 0-1 R^4, C_2-C_7 alkenylene, or C_2-C_7 alkynylene;

Y is selected from:
hydroxy,
C_1 to C_{10} alkyloxy,
C_3 to C_{11} cycloalkyloxy,
C_6 to C_{10} aryloxy,
C_7 to C_{11} aralkyloxy,
C_3 to C_{10} alkylcarbonyloxyalkyloxy,
C_3 to C_{10} alkoxycarbonyloxyalkyloxy,
C_2 to C_{10} alkoxycarbonylalkyloxy,
C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonylalkyloxy,
C_7 to C_{11} aryloxycarbonylalkyloxy,
C_8 to C_{12} aryloxycarbonyloxyalkyloxy,
C_8 to C_{12} arylcarbonyloxyalkyloxy,
C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy,
C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or
C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

Z is selected from O or CH_2;

D, E, F and G are each independently selected from:
CH_2;
carbonyl;
a heteroatom moiety selected from N, NH, O, provided that no more than 2 of D, E, F and G are N, NH, O or S;
alternatively, the bond between D and E, E and F, or F and G in such spiro-fused ring may be a carbon-nitrogen double bond or a carbon-carbon double bond;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylsulfonyl, heteroarylcarbonyl, heteroaryalkylcarbonyl or aryl;

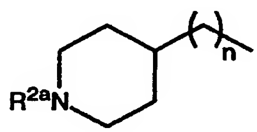
n is 0-4;
p is 1-3;
q is 1-7;
r is 0-3;

provided that n, p, q and r are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

18. A compound of Claim 17 wherein:

R^1 is $R^2NHC(=NR^2)$- and V is phenyl or pyridyl or

R^1 is



and V is a single bond;

n is 1 or 2;

X is C_1-C_4 alkylene substituted with 0-1 R^4;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;

1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{12} and R^{13} are each independently selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, heteroarylsulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl; and

R^{13} is H.

19. A compound of Claim 16, or pharmaceutically acceptable salt forms thereof, selected from:

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;
5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;
5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;
5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5(*R*,*S*)-3-(4-amidinophenyl)-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-7,9-dione;

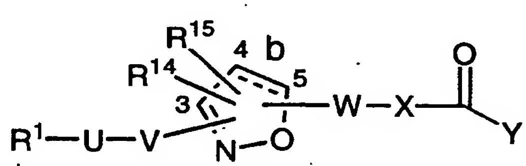
5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]non-2-ene-5-one;

5(*R*,*S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;

5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]nona-2,8-diene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-7,9-dione;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5,7-dione;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]dec-2-ene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]deca-2,8-diene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-7,9-dione;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2,8-diazaspiro[4.4]undec-2-ene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(2-carboxyethyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;
5(*R,S*)-3-[2-(piperidin-4-yl)ethyl]-8-(3-carboxypropyl)-1-oxa-2-azaspiro[4.4]undeca-2,8-diene-5-one;
5(R,S)-3-(4-amidinophenyl)-8-[2-(benzyloxycarbonylamino)-2-carboxyethyl]-1-oxa-2,8-diazaspiro[4.5]dec-2-ene.

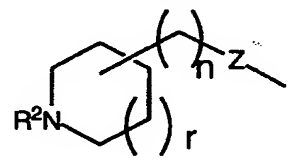
20. A compound of Formula I:



(I)

or pharmaceutically acceptable salt form thereof, wherein:
b is a carbon-carbon single bond or double bond;

R^1 is selected from:
$R^2(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N=)C(CH_2)_qZ-$,
$R^2(R^3)N(R^2N=)CN(R^2)(CH_2)_qZ-$, piperazinyl-$(CH_2)_qZ-$ or



;

Z is selected from O, S, S(=O), $S(=O)_2$;

R^2 and R^3 are independently selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl, C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl;

U is optionally present and is selected from C_1-C_7 alkylene, C_2-C_7 alkenylene, C_2-C_7 alkynylene, arylene, or pyridylene;

V is selected from:
a single bond;
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-4 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

W is -(aryl)-Z^1-, wherein said aryl is substituted with 0-6 R^6 or R^7;

Z^1 is selected from a single bond, $-CH_2-$, O or S;

X is selected from:
a single bond;
C_1-C_7 alkylene substituted with 0-6 R^4, R^8 or R^{15};
C_2-C_7 alkenylene substituted with 0-4 R^4, R^8 or R^{15};
C_2-C_7 alkynylene substituted with 0-4 R^4, R^8 or R^{15};

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy; $(R^2)(R^3)N-(C_1$-C_{10} alkoxy$)-$;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^{5a}, $C(=O)R^{5a}$, $CONHR^{5a}$, $CON(R^{12})_2$, $OC(=O)R^{5a}$, $OC(=O)OR^{5a}$, OR^{5a}, $OC(=O)N(R^{12})_2$, $OCH_2CO_2R^{5a}$, $CO_2CH_2CO_2R^{5a}$, $N(R^{12})_2$, NO_2, $NR^{12}C(=O)R^{5a}$, $NR^{12}C(=O)OR^{5a}$, $NR^{12}C(=O)N(R^{12})_2$, $NR^{12}SO_2N(R^{12})_2$, $NR^{12}SO_2R^{5a}$, $S(O)_pR^{5a}$, $SO_2N(R^{12})_2$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with halogen, alkoxy, alkyl, $-CF_3$, $S(O)_mMe$, or $-NMe_2$; or

C_7 to C_{11} arylalkyl said aryl being optionally substituted with halogen, alkoxy, alkyl, $-CF_3$, $S(O)_mMe$, or $-NMe_2$;

R^8 is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_2-C_{10} alkynyl, substituted with 0-6 R^6;
C_3-C_8 cycloalkyl, substituted with 0-6 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-5 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, heteroarylsulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_2-C_7 alkylcarbonyl, C_7-C_{11} arylcarbonyl, C_2-C_{10} alkoxycarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl or aryl(C_1-C_{10} alkoxy)carbonyl;

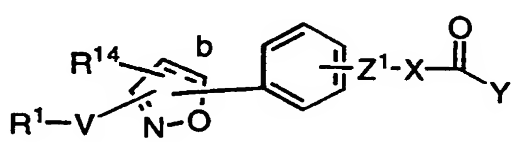
R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^{12})R^{13}$;

R^5 and R^{5a} are selected independently from H, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, C_7 to C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-8 R^4;

R^{15} is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-8 R^6;
C_2-C_{10} alkenyl, substituted with 0-6 R^6;
C_1-C_{10} alkoxy, substituted with 0-6 R^6;
aryl, substituted with 0-5 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-5 R^6;
C_1-C_{10} alkoxycarbonyl substituted with 0-8 R^6;
CO_2R^5; or
$-C(=O)N(R^{12})R^{13}$;

n is 0-4;
q is 2-7;
r is 0-3;
provided that n, q, and r are chosen such that the number of atoms between R^1 and Y is about 8-17.

21. A compound of Claim 20 of Formula IV:

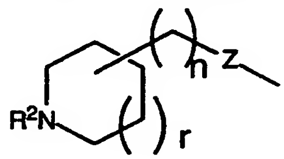


(IV)

wherein:

b is a carbon-carbon single bond or double bond;

R^1 is selected from $R^2HN(CH_2)_qO-$, $R^2HN(R^2N{=}C)NH(CH_2)_qO-$, piperazinyl-$(CH_2)_qO-$, or



;

Z is O;

R^2 is selected from H, aryl(C_1-C_{10})alkoxycarbonyl, C_1-C_{10} alkoxycarbonyl;

V is selected from:
a single bond;
C_1-C_7 alkylene substituted with 0-6 R^6 or R^7;
C_2-C_7 alkenylene substituted with 0-4 R^6 or R^7;
C_2-C_7 alkynylene substituted with 0-4 R^6 or R^7;
phenylene substituted with 0-3 R^6 or R^7;
pyridylene substituted with 0-3 R^6 or R^7;
pyridazinylene substituted with 0-3 R^6 or R^7;

Z^1 is selected from a single bond, O or S;

X is selected from:
a single bond;
C_1-C_7 alkylene substituted with 0-4 R^4, R^8 or R^{15};
C_2-C_7 alkenylene substituted with 0-3 R^4, R^8 or R^{15};
C_2-C_7 alkynylene substituted with 0-3 R^4, R^8 or R^{15};

Y selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10}

cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, or C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R^4 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, or $-N(R^{12})R^{13}$;

R^6 and R^7 are selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^8 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, C_5-C_6 cycloalkenyl, aryl, 5-6 membered heterocyclic ring containing 1-2 N, O, or S, where said heterocyclic ring may be saturated, partially saturated, or fully unsaturated;

R^{12} and R^{13} are independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylsulfonyl, heteroarylalkylcarbonyl or aryl;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^{12})R^{13}$;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^4;

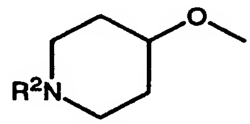
n is 0-4;

q is 2-7;

provided that n and q are chosen such that the number of atoms between R^1 and Y is in the range of 8-17.

22. A compound of Claim 21 wherein:

R^1 is $R^2HN(CH_2)_qO$- or



V is C_1-C_3 alkylene;

Z^1 is a single bond or O;

X is C_1-C_3 alkylene substituted with 0-1 R^4;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;

1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

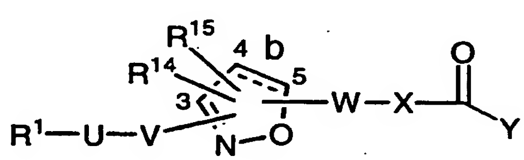
R^{12} and R^{13} are independently selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_4 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, heteroarylcarbonyl, heteroarylsulfonyl, heteroarylalkylcarbonyl or aryl;

R^{13} is H.

23. A compound of Claim 20, or a pharmaceutically acceptable salt form thereof, selected from:

5(*R,S*)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-yl]hydrocinnamic acid;
5(*R,S*)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]hydrocinnamic acid;
5(*R,S*)-4-[3-(3-aminopropyloxymethyl)isoxazolin-5-yl]hydrocinnamic acid;
5(*R,S*)-4-[3-(piperidin-4-yl)oxymethylisoxazolin-5-yl]phenoxyacetic acid;
5(*R,S*)-4-[3-(2-aminoethoxymethyl)isoxazolin-5-yl]phenoxyacetic acid;
5(*R,S*)-4-[3-(3-aminopropyloxymethyl)isoxazolin-5-yl]phenoxyacetic acid.

24. A compound of Formula I:

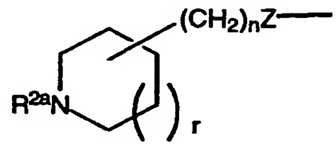
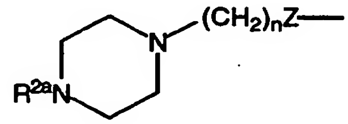


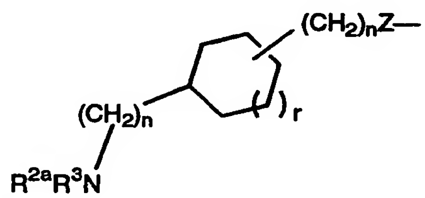
(I)

or a pharmaceutically acceptable salt form thereof wherein:

b is a carbon-carbon single or double bond;

R^1 is selected from $R^{2a}(R^3)N-$, $R^2(R^3)N(R^2N{=})C-$, $R^{2a}(R^3)N(CH_2)_qZ-$, $R^2(R^3)N(R^2N{=})C(CH_2)_qZ-$, $R^2(R^3)NC(O)-$, $R^2(R^5O)N(R^2N{=})C-$, $R^2(R^3)N(R^5ON{=})C-$;


,

or


;

Z is selected from a bond, O, S, S(=O), $S(=O)_2$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;
aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is

optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

provided that only one of R^2 and R^3 may be hydroxy;

R^{2a} is R^2 or $R^2(R^3)N(R^2N{=})C$;

U is selected from:
- a single bond,
- $-(C_1$-C_7 alkyl$)-$,
- $-(C_2$-C_7 alkenyl$)-$,
- $-(C_2$-C_7 alkynyl$)-$,
- -(aryl)- substituted with 0-3 R^{6a}, or
- -(pyridyl)- substituted with 0-3 R^{6a};

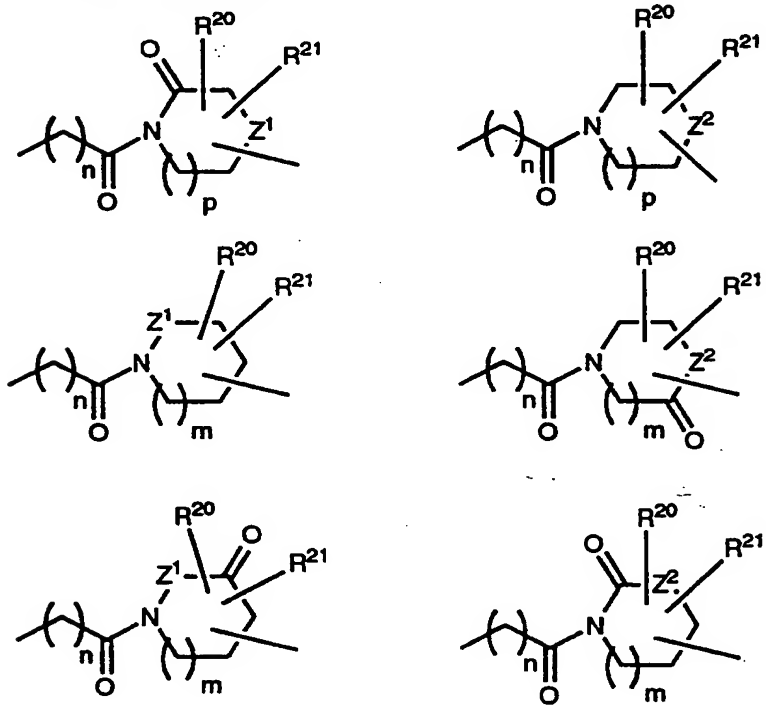
V is selected from:
- a single bond;
- $-(C_1$-C_7 alkyl$)-$, substituted with 0-3 groups independently selected from R^6 or R^7;
- $-(C_2$-C_7 alkenyl$)-$, substituted with 0-3 groups independently selected from R^6 or R^7;
- $-(C_2$-C_7 alkynyl$)-$, substituted with 0-3 groups independently selected from R^6 or R^7;

-(phenyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

-(pyridyl)-, substituted with 0-2 groups independently selected from R^6 or R^7; or

-(pyridazinyl)-, substituted with 0-2 groups independently selected from R^6 or R^7;

W is selected from:



;

X is selected from:

a single bond,

$-(C(R^4)_2)_n-C(R^4)(R^8)-C(R^4)(R^{4a})-$,

with the proviso that when n is 0 or 1, then at least one of R^{4a} or R^8 is other than H or methyl;

Y selected from:

hydroxy,

C_1 to C_{10} alkyloxy,

C_3 to C_{11} cycloalkyloxy,

C_6 to C_{10} aryloxy,

C_7 to C_{11} aralkyloxy,

C_3 to C_{10} alkylcarbonyloxyalkyloxy,
C_3 to C_{10} alkoxycarbonyloxyalkyloxy,
C_2 to C_{10} alkoxycarbonylalkyloxy,
C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy,
C_5 to C_{10} cycloalkoxycarbonylalkyloxy,
C_7 to C_{11} aryloxycarbonylalkyloxy,
C_8 to C_{12} aryloxycarbonyloxyalkyloxy,
C_8 to C_{12} arylcarbonyloxyalkyloxy,
C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy,
C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy,
$(R^2)(R^3)N-(C_1-C_{10}$ alkoxy)-;

Z^1 is -C-, -O-, or $-NR^{22}-$;

Z^2 is -O-, or $-NR^{22}-$;

R^4 is selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkylene cycloalkyl, or cycloalkylalkylene;

alternately, two R^4 groups on adjacent carbon atoms may join to form a bond, thereby to form a carbon-carbon double or triple bond between such adjacent carbon atoms;

R^{4a} is selected from H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$,
C_1-C_{10} alkyl substituted with 0-3 R^6,
aryl substituted with 0-3 R^6, or
C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6

alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, -N(R^{12})R^{13}; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, or pyridyl;

R^5 is selected from H, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, C_7 to C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

alternately, R^5 and R^{5a} when both are substituents on the same nitrogen atom (as in -NR^5R^{5a}) can be taken together with the nitrogen atom to which they are attached to form 3-azabicyclononyl, 1,2,3,4-tetrahydro-1-quinolinyl, 1,2,3,4-tetrahydro-2-isoquinolinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl or 1-piperazinyl, each being optionally substituted with C_1-C_6 alkyl, C_6-C_{10} aryl, heteroaryl, C_7-C_{11} arylalkyl, C_1-C_6 alkylcarbonyl, C_3-C_7 cycloalkylcarbonyl, C_1-C_6 alkoxycarbonyl, C_7-C_{11} arylalkoxycarbonyl, C_1-C_6 alkylsulfonyl or C_6-C_{10} arylsulfonyl;

R^{5b} is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, C_7-C_{11} arylalkyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, -N(R^{12})R^{13},

cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^5, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_pR^5$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

C_7 to C_{11} arylalkyl, said aryl being optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substiuent on aryl; or

a 5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^7;

R^{6a} is selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, NO_2, or $NR^{12}R^{13}$;

R^7 is selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, halo, CF_3, CHO, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $OC(=O)R^{5a}$, $OC(=O)OR^{5b}$, OR^{5a}, $OC(=O)NR^5R^{5a}$, $OCH_2CO_2R^5$, $CO_2CH_2CO_2R^5$, NO_2, $NR^{5a}C(=O)R^{5a}$, $NR^{5a}C(=O)OR^{5b}$, $NR^{5a}C(=O)NR^5R^{5a}$, $NR^{5a}SO_2NR^5R^{5a}$, $NR^{5a}SO_2R^5$, $S(O)_mR^{5a}$, $SO_2NR^5R^{5a}$, C_2 to C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_6 to C_{10} aryl, or C_7 to C_{11} arylalkyl;

R^8 is selected from:

R^6;
C_2-C_{10} alkyl, substituted with 0-3 R^6;
C_2-C_{10} alkenyl, substituted with 0-3 R^6;
C_2-C_{10} alkynyl, substituted with 0-3 R^6;
C_3-C_8 cycloalkyl, substituted with 0-3 R^6;
C_5-C_6 cycloalkenyl, substituted with 0-3 R^6;
aryl, substituted with 0-3 R^6;
5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, heteroarylsulfonyl, arylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_7-C_{11} arylcarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, or aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{14} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{15} is selected from:
H;
R^6;
C_1-C_{10} alkyl, substituted with 0-3 R^6;
C_2-C_{10} alkenyl, substituted with 0-3 R^6;
C_1-C_{10} alkoxy, substituted with 0-3 R^6;
aryl, substituted with 0-3 R^6;

5-6 membered heterocyclic ring containing 1-2 N, O, or S heteroatoms, wherein said heterocyclic ring may be saturated, partially saturated, or fully unsaturated, said heterocyclic ring being substituted with 0-2 R^6;

C_1-C_{10} alkoxycarbonyl substituted with 0-2 R^6;

$-CO_2R^5$; or

$-C(=O)N(R^{12})R^{13}$;

provided that when b is a double bond, only one of R^{14} or R^{15} is present;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-C(=O)N(R^{18b})_2$,

$-C(=O)NHSO_2R^{18a}$,

$-C(=O)NHC(=O)R^{18b}$,

$-C(=O)NHC(=O)OR^{18a}$,

$-C(=O)NHSO_2NHR^{18b}$,

$-C(=S)-NH-R^{18b}$,

$-NH-C(=O)-O-R^{18a}$,

$-NH-C(=O)-R^{18b}$,

$-NH-C(=O)-NH-R^{18b}$,

$-SO_2-O-R^{18a}$,

$-SO_2-R^{18a}$,

$-SO_2-N(18^b)_2$,

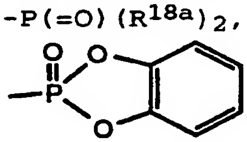
$-SO_2-NHC(=O)O18^b$,

$-P(=S)(OR^{18a})_2$,

$-P(=O)(OR^{18a})_2$,

$-P(=S)(R^{18a})_2$,

$-P(=O)(R^{18a})_2$, or



;

R^{17} is selected from: H, C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10} alkyl)-;

R^{18a} is selected from:
C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19},

C_1-C_6 alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

R^{20} and R^{21} are each independently selected from H, C_1-C_{10} alkyl, CO_2R^5, $C(=O)R^{5a}$, $CONR^5R^{5a}$, $NR^5C(=O)R^{5a}$, $NR^{12}R^{13}$, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylmethyl, C_6-C_{10} aryl, or C_7-C_{11} arylalkyl;

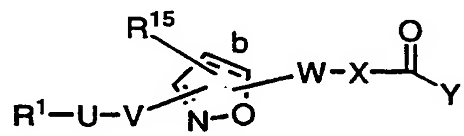
R^{22} is selected from C_1-C_{10} alkyl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{15} cycloalkylalkyl, aryl, aryl(C_1-C_{10}

alkyl)-; $C(=O)R^{5a}$, CO_2R^{5b}, $-C(=O)N(R^5)R^{5a}$, or a bond to X;

m is 0-2;
n is 0-2;
p is 1-2;
q is 1-7;
r is 0-3;

provided that n, q and r are chosen such that the number of atoms connecting R^1 and Y is in the range of 8-17.

25. A compound of Claim 24 of Formula Ic:



(Ic) .

wherein:

Z is selected from a bond, O, or S;

R^2 and R^3 are independently selected from: H; C_1-C_6 alkyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl wherein the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

U is a single bond;

X is $-CHR^{4a}-$;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-6 R^{4b};

R^6 and R^7 are each independently selected from H, C_1-C_{10} alkyl, hydroxy, C_1-C_{10} alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, cyano, or halo;

R^{12} and R^{13} are each independently selected from H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, heteroarylsulfonyl, or aryl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{15} is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, aryl, heteroaryl or C_1-C_{10} alkoxycarbonyl, CO_2R^5 or $-C(=O)N(R^5)R^{5a}$;

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,
$-C(=O)-R^{18b}$,
$-S(=O)_2-R^{18a}$;

R^{17} is selected from: H or C_1-C_4 alkyl;

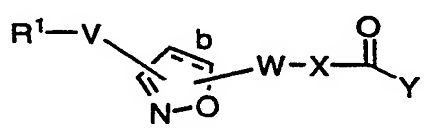
R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-2 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-2 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19}.

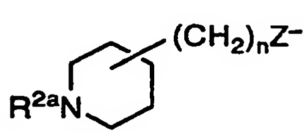
26. A compound of Claim 24 of Formula Ib:



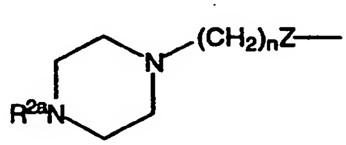
(Ib)

wherein:

R^1 is selected from: $R^2(R^3)N$-, $R^2NH(R^2N=)C$-, $R^2R^3N(CH_2)_{p'}Z$-, $R^2NH(R^2N=)CNH(CH_2)_{p'}Z$-, $R^2(R^3)NC(O)$-, $R^2(R^5O)N(R^2N=)C$-, $R^2(R^3)N(R^5ON=)C$-;



, or



;

n is 0-1;
p' is 2-4;
p" is 4-6;

Z is selected from a bond or O;

R^3 is H or C_1-C_5 alkyl;

V is a single bond, or
-(phenyl)-;

X is selected from:
$-CH_2-$,
$-CHN(R^{16})R^{17}-$, or
$-CHNR^5R^{5a}-$;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;
methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;

(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{18a} is selected from:
C_1-C_4 alkyl substituted with 0-2 R^{19},
C_2-C_4 alkenyl substituted with 0-2 R^{19},
C_2-C_4 alkynyl substituted with 0-2 R^{19},
C_3-C_4 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-2 R^{19},
aryl(C_1-C_4 alkyl)- substituted with 0-2 R^{19},

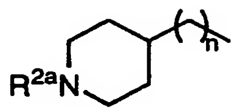
a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^{19}.

27. A compound of Claim 26 wherein:

R^1 is $R^2NH(R^2N{=})C$- or $R^2NH(R^2N{=})CNH$- and V is phenyl or pyridyl; or

R^1 is



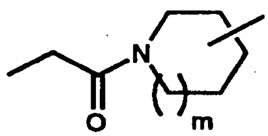
, and V is a single bond;

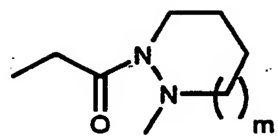
n is 1-2;

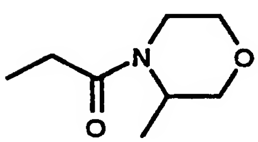
R^3 is H or C_1-C_5 alkyl;

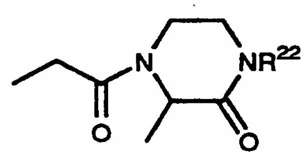
X is selected from:
-CH_2-,
-$CHN(R^{16})R^{17}$-, or
-$CHNR^5R^{5a}$-;

W is selected from:

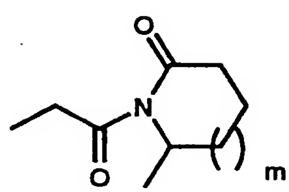








or



;

m is 1-3;

Y is selected from:
hydroxy;
C_1 to C_{10} alkoxy;

methylcarbonyloxymethoxy-;
ethylcarbonyloxymethoxy-;
t-butylcarbonyloxymethoxy-;
cyclohexylcarbonyloxymethoxy-;
1-(methylcarbonyloxy)ethoxy-;
1-(ethylcarbonyloxy)ethoxy-;
1-(t-butylcarbonyloxy)ethoxy-;
1-(cyclohexylcarbonyloxy)ethoxy-;
i-propyloxycarbonyloxymethoxy-;
t-butyloxycarbonyloxymethoxy-;
1-(i-propyloxycarbonyloxy)ethoxy-;
1-(cyclohexyloxycarbonyloxy)ethoxy-;
1-(*t*-butyloxycarbonyloxy)ethoxy-;
dimethylaminoethoxy-;
diethylaminoethoxy-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(5-(*t*-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methoxy-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methoxy-;
1-(2-(2-methoxypropyl)carbonyloxy)ethoxy-;

R^{19} is H, halogen, C_1-C_4 alkyl, C_3-C_7 cycloalkyl, cyclopropylmethyl, aryl, or benzyl;

R^{20} and R^{21} are both H;

R^{22} is H, C_1-C_4 alkyl or benzyl.

28. A compond of Claim 24, or a pharmaceutically acceptable salt form thereof, selected from:

2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperidine;
2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azepine;
2-(R,S)-2-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine;

3-(R,S)-carboxymethyl-4-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperazine-2-one;

6-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]piperidine-2-one;

5-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrrolidine-2-one;

7-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]azetidine-2-one;

2-(R,S)-carboxymethyl-1-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]pyrazolidine;

3-(R,S)-carboxymethyl-4-{5-(R,S)-N-[3-(4-amidinophenyl)isoxazolin-5-yl acetyl]morpholine.

29. A method for the prevention or treatment of thrombosis which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1, 6, 11, 16, 20, or 24.

30. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 6, 11, 16, 20, or 24 and a pharmaceutically acceptable carrier.

31. A method of inhibiting the aggregation of blood platelets which comprises administering to a host in need of such inhibition a therapeutically effective amount of a compound of Claim 1, 6, 11, 16, 20, or 24 .

32. A method of treating thromboembolic disorders selected from thrombus or embolus formation, harmful platelet aggregation, reocclusion following thrombolysis, reperfusion injury, restenosis, atherosclerosis, stroke, myocardial infarction, and unstable angina, which comprises administering to a host in need of such

treatment a therapeutically effective amount of a compound of Claim 6.

33. A method for the treatment of thrombosis which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 6 in combination with one or more additional therapeutic agents selected from: a thrombolytic agent, an anti-coagulant agent, or an anti-platelet agent.

34. A method of treating rheumatoid arthritis, asthma, allergies, adult respiratory syndrome, organ transplantation rejection, septic shock, psoriasis, contact dermatitis, osteoporosis, osteoarthritis, tumor metastasis, diabetic retinopathy, inflammatory conditions and inflammatory bowel disease, comprising administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 6.

35. A compound of Claim 6, or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt form thereof, selected from:

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(phenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methyl-phenyl-sulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(butanesulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(propanesulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(ethanesulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(ethyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(1-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(1-(2-methyl)-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(2-methyl)-propyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(benzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methylbenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methoxybenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-chlorobenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-bromobenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-fluorobenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-phenoxybenzyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(methyloxyethyl)-oxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-pyridinylcarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-pyridinylcarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-pyridinyl-carbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(2-pyridinyl)-acetyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(3-pyridinyl)-acetyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-(4-pyridinyl)-acetyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-pyridyl-methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-pyridyl-methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-pyridyl-methyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-butyloxyphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-thienylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-iodophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-trifluoromethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-chlorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-methoxycarbonylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2,4,6-trimethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-chlorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-trifluoromethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-trifluoromethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-fluorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-fluorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-methoxyphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2,3,5,6-tetramethylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-cyanophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-chlorophenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-propylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-phenylethylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-isopropylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-phenylpropylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-pyridylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(phenylaminosulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(benzylaminosulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(dimethylaminosulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(phenylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-fluorophenylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(1-naphthylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(benzylaminocarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-bromo-2-thienylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methyl-2-benzothienylsulfonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(isobutyloxycarbonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-cyclopropylethoxycarbonyl)-2,3-diaminopropanoic acid,

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-guanidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropanoic acid;

N^3-[2-{5-(4-formamidinophenyl)-isoxazolin-3-yl}-acetyl]-N^2-(n-butyloxycarbonyl)-2,3-diaminopropanoic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(2-methyl-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(3-formamidino-6-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(2-formamidino-5-pyridinyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(2-fluoro-4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-methylphenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(3-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

N^3-[2-{3-(4-formamidinophenyl)-isoxazolin-5-yl}-acetyl]-N^2-(4-bromo-phenylsulfonyl)-2,3-diaminopropionic acid;

said enantiomeric and diasteriomeric forms being selected from:

(*R*,*S*), (*R*,*S*);
(*R*), (*R*,*S*);
(*S*), (*R*,*S*);
(*R*), (*R*);
(*S*), (*R*);
(*R*), (*S*);
(*S*), (*S*).

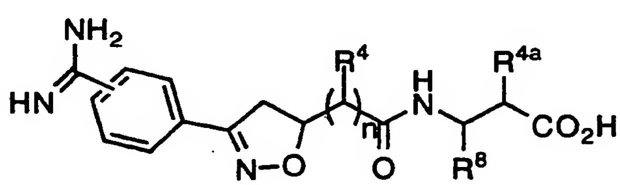
36. A compound of Claim 35, or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt form thereof, said enantiomeric and diasteriomeric form being: (*R*), (*S*).

37. A prodrug ester of a compound of Claim 35, or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt form thereof, said ester being selected from the group consisting of:

methyl;
ethyl;
isopropyl;
methylcarbonyloxymethyl-;
ethylcarbonyloxymethyl-;
t-butylcarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
1-(methylcarbonyloxy)ethyl-;
1-(ethylcarbonyloxy)ethyl-;
1-(t-butylcarbonyloxy)ethyl-;
1-(cyclohexylcarbonyloxy)ethyl-;
i-propyloxycarbonyloxymethyl-;
cyclohexylcarbonyloxymethyl-;
t-butyloxycarbonyloxymethyl-;
1-(i-propyloxycarbonyloxy)ethyl-;
1-(cyclohexyloxycarbonyloxy)ethyl-;
1-(t-butyloxycarbonyloxy)ethyl-;
dimethylaminoethyl-;
diethylaminoethyl-;
(5-methyl-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(5-(t-butyl)-1,3-dioxacyclopenten-2-on-4-yl)methyl-;
(1,3-dioxa-5-phenyl-cyclopenten-2-on-4-yl)methyl-;
1-(2-(2-methoxypropyl)carbonyloxy)ethyl-.

38. A prodrug ester of a compound of Claim 36, said ester being selected from the group consisting of:
methyl;
ethyl;
isopropyl.

39. A process for preparing a compound of the formula X



(X)

wherein:

R^4 is selected from: H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{4a} is selected from: H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, or C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_7-C_{14} bicycloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{12})R^{13}$; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3-C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, $-NR^5R^{5a}$, CO_2R^5, $S(O)_mR^5$, OR^5, cyano, halo;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl,

benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolyl, isoxazolinyl or morpholinyl;

R^8 is selected from:

$-CONR^5NR^{5a}$; $-CO_2R^5$;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6,

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

aryl, substituted with 0-2 R^6;

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} is selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, arylsulfonyl, aryl, heteroarylsulfonyl, pyridylcarbonyl or pyridylmethylcarbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2; and

R^{13} is H.

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-C(=O)N(R^{18b})_2$,

$-SO_2-R^{18a}$, or

$-SO_2-N(R^{18b})_2$;

R^{17} is selected from: H or C_1-C_4 alkyl

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},

C_2-C_8 alkenyl substituted with 0-2 R^{19},

C_2-C_8 alkynyl substituted with 0-2 R^{19},

C_3-C_8 cycloalkyl substituted with 0-2 R^{19},

aryl substituted with 0-4 R^{19},

aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

m is 0-2;

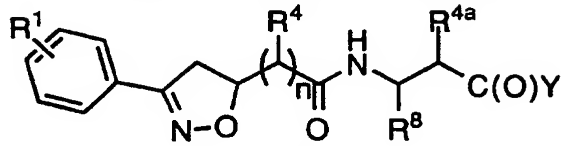
n is 0-4;

q is 1-7; and

r is 0-3;

said process comprising the steps of:

deprotecting a compound of the formula IX



(IX)

wherein:

R^1 is $HR^2N-C(=NR^2)-$, $NC-$, $HR^2N-C(=NHR^2)-NH-$, or HR^2N-;

R^2 and R^3 are independently H, C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl wherein the heteroaryl group is optionally substituted with 0-2 groups selected

from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

Y is selected from C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, $(R^2)(R^3)N-(C_1$-C_{10} alkoxy)-;

m is 0-2;

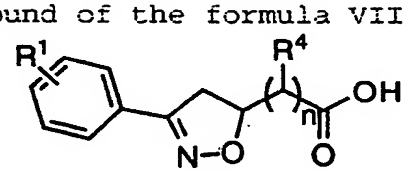
n is 0-4; and

all other substituents are as defined above;

under acidic, basic, catalytic, and/or enzymatic conditions to provide a compound of formula (X) as defined above.

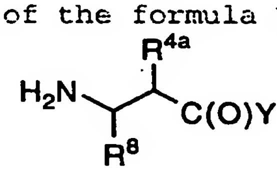
40. A process according to Claim 39 further comprising the step of:

contacting a compound of the formula VII



(VII)

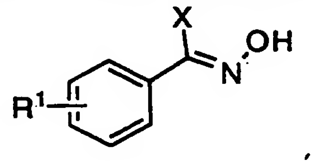
with a compound of the formula VIII



(VIII)

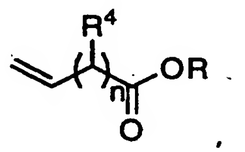
under peptide bond forming conditions to effect the formation of a peptide bond and form a compound of the formula (IX) wherein all substituents are as defined in Claim 39.

41. A process according to Claim 40 further comprising the steps of:
contacting a compound of the formula V



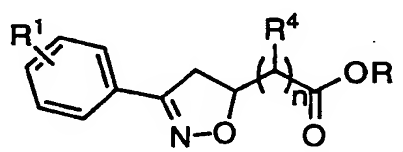
(V)

wherein X is chloro, bromo or iodo, in the presence of a hindered amine base with a compound of the formula VI



(VI)

wherein R is alkyl or other group removable under basic conditions to form a compound of the formula VIIa



(VIIa)

wherein all other substituents are as defined in Claim 40; and
hydrolyzing a compound of the formula VIIa under mild basic conditions to form a compound of the formula VII.

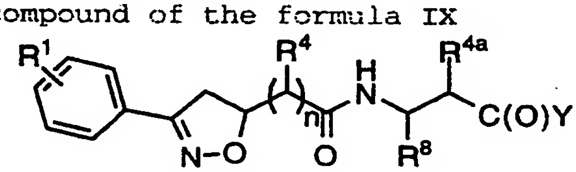
42. A process according to Claim 40 further comprising the step of:

resolving the two stereoisomers of a compound of the formula VII, wherein R^4 is H, by chemical resolution with an appropriate optically pure chiral amine to form the separated (+) and (-) isomers of a compound of the formula VII.

43. A process according to Claim 40 further comprising the step of:
resolving the two stereoisomers of a compound of the formula VII by chiral chromatography to form the separated (+) and (-) isomers of a compound of the formula VII.

44. A process according to Claim 40 further comprising the step of:
resolving the two stereoisomers of a compound of the formula VIIa by chiral chromatography to form the separated (+) and (-) isomers of a compound of the formula VIIa.

45. A compound of the formula IX



(IX)

wherein:
Y is selected from C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10}

alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy;

R^1 is NC-;

R^4 is selected from: H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{4a} is selected from: H, hydroxy, C_1-C_{10} alkoxy, nitro, $N(R^5)R^{5a}$, $-N(R^{12})R^{13}$, $-N(R^{16})R^{17}$, C_1-C_{10} alkyl substituted with 0-3 R^6, aryl substituted with 0-3 R^6, or C_1-C_{10} alkylcarbonyl;

R^{4b} is selected from: H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_7 cycloalkyl, C_7-C_{14} bicycloalkyl, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, nitro, C_1-C_6 alkylcarbonyl, C_6-C_{10} aryl, $-N(R^{12})R^{13}$; halo, CF_3, CN, C_1-C_6 alkoxycarbonyl, carboxy, piperidinyl, morpholinyl or pyridinyl;

R^5 is selected from H or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^{5a} is selected from hydrogen, hydroxy, C_1 to C_8 alkyl, C_3-C_6 alkenyl, C_3 to C_{11} cycloalkyl, C_4 to C_{11} cycloalkylmethyl, C_1-C_6 alkoxy, benzyloxy, C_6 to C_{10} aryl, heteroaryl, heteroarylalkyl, C_7 to C_{11} arylalkyl, adamantylmethyl, or C_1-C_{10} alkyl substituted with 0-2 R^{4b};

R^6 is selected from H, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, nitro, C_1-C_{10} alkylcarbonyl, $-N(R^{12})R^{13}$, $-NR^5R^{5a}$, CO_2R^5, $S(O)_mR^5$, OR^5, cyano, halo;

C_6 to C_{10} aryl optionally substituted with 1-3 groups selected from halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mMe$, or $-NMe_2$;

methylenedioxy when R^6 is a substituent on aryl; or

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, isoxazolyl, isoxazolinyl or morpholinyl;

R^8 is selected from:

$-CONR^5NR^{5a}$; $-CO_2R^5$;

C_1-C_{10} alkyl, substituted with 0-3 R^6;

C_2-C_{10} alkenyl, substituted with 0-3 R^6;

C_2-C_{10} alkynyl, substituted with 0-3 R^6,

C_3-C_8 cycloalkyl, substituted with 0-3 R^6;

aryl, substituted with 0-2 R^6;

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-2 R^6;

R^{12} is selected from H, C_1-C_6 alkyl, C_1-C_4 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylsulfonyl, aryl(C_1-C_4 alkyl)sulfonyl, heteroarylsulfonyl, arylsulfonyl, aryl, pyridylcarbonyl or pyridylmethylcarbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2; and

R^{13} is H.

R^{16} is selected from:

$-C(=O)-O-R^{18a}$,

$-C(=O)-R^{18b}$,

$-C(=O)N(R^{18b})_2$,
$-SO_2-R^{18a}$, or
$-SO_2-N(R^{18b})_2$;

R^{17} is selected from: H or C_1-C_4 alkyl

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, triazolyl, imidazolyl, benzofuranyl, indolyl, indolinyl, quinolinyl, isoquinolinyl, isoxazolyl, isoxazolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyrimidinyl, 3*H*-indolyl, carbazolyl, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

C_1-C_6 alkyl substituted with a heterocyclic ring system selected from pyridinyl, furanyl, thiazolyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, isoxazolyl, isoxazolinyl, benzofuranyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, tetrahydrofuranyl, pyranyl, pyridinyl, 3*H*-indolyl, indolyl, carbazole, pyrrolidinyl, piperidinyl, indolinyl, or morpholinyl, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

m is 0-2;

n is 0-4;
q is 1-7; and
r is 0-3.

46. A compound of the formulae VII or VIIa wherein:

R is H, alkyl, or other group removable under basic conditions;

R^1 is $HR^2N-C(=NR^2)-$, NC-, $HR^2N-C(=NHR^2)-NH-$, or HR^2N-;

R^2 is H, C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from

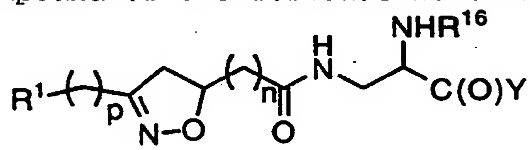
hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

R^4 is selected from: H, C_1-C_{10} alkyl, C_1-C_{10} alkylcarbonyl, aryl, arylalkyl, cycloalkyl, or cycloalkylalkyl;

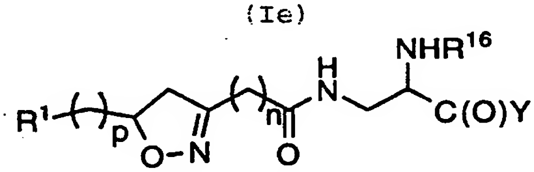
m is 0-2;

n is 0-4;

47. A compound of the formulae Ie or If



(Ie)



(If)

or enantiomeric or diasteriomeric forms thereof, or mixtures of enantiomeric or diasteriomeric forms thereof, or a pharmaceutically acceptable salt form thereof, wherein:

R^1 is $R^2(R^3)N(R^2N=)C-$, $R^2(R^3)N(R^2N=)CN(R^2)-$, or $R^2(R^3)N-$;

R^2 and R^3 are independently selected from: H; C_1-C_{10} alkyl; C_3-C_6 alkenyl; C_3-C_{11} cycloalkyl; C_4-C_{11} cycloalkylalkyl; C_6-C_{10} aryl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_7-C_{11} arylalkyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_2-C_7 alkylcarbonyl; C_7-C_{11} arylcarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl,

ethylenedioxydiyl; C_1-C_{10} alkoxycarbonyl; C_4-C_{11} cycloalkoxycarbonyl; C_7-C_{11} bicycloalkoxycarbonyl; C_7-C_{11} aryloxycarbonyl optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; aryl(C_1-C_{10} alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_1-C_6 alkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; C_6-C_{10} arylcarbonyloxy(C_1-C_4 alkoxy)carbonyl where the aryl group is optionally substituted with 0-3 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; C_4-C_{11} cycloalkylcarbonyloxy(C_1-C_4 alkoxy)carbonyl; heteroaryl optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl; or heteroaryl(C_1-C_5)alkyl where the heteroaryl group is optionally substituted with 0-2 groups selected from hydroxy, halogen, C_1-C_6 alkoxy, C_1-C_6 alkyl, CF_3, $S(O)_mCH_3$, $-N(CH_3)_2$, C_1-C_4 haloalkyl, methylenedioxydiyl, ethylenedioxydiyl;

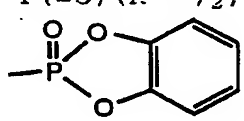
provided that only one of R^2 and R^3 may be hydroxy;

R^{12} and R^{13} are independently H, C_1-C_{10} alkyl, C_1-C_{10} alkoxycarbonyl, C_1-C_{10} alkylcarbonyl, C_1-C_{10} alkylsulfonyl, aryl(C_1-C_{10} alkyl)sulfonyl, arylsulfonyl, aryl(C_2-C_{10} alkenyl)sulfonyl, heteroarylsulfonyl, aryl, C_2-C_6 alkenyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, C_7-C_{11} arylalkyl, C_7-C_{11} arylcarbonyl, C_4-C_{11} cycloalkoxycarbonyl, C_7-C_{11} bicycloalkoxycarbonyl, C_7-C_{11} aryloxycarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl, or

aryl(C_1-C_{10} alkoxy)carbonyl, wherein said aryls are optionally substituted with 0-3 substituents selected from the group consisting of: C_1-C_4 alkyl, C_1-C_4 alkoxy, halo, CF_3, and NO_2;

R^{16} is selected from:

-C(=O)-O-R^{18a},
-C(=O)-R^{18b},
-C(=O)N(R^{18b})$_2$,
-C(=O)NHSO$_2$$R^{18a}$,
-C(=O)NHC(=O)R^{18b},
-C(=O)NHC(=O)OR^{18a},
-C(=O)NHSO$_2$NHR^{18b},
-C(=S)-NH-R^{18b},
-NH-C(=O)-O-R^{18a},
-NH-C(=O)-R^{18b},
-NH-C(=O)-NH-R^{18b},
-SO$_2$-O-R^{18a},
-SO$_2$-R^{18a},
-SO$_2$-N(18^b)$_2$,
-SO$_2$-NHC(=O)O18^b,
-P(=S)(OR^{18a})$_2$,
-P(=O)(OR^{18a})$_2$,
-P(=S)(R^{18a})$_2$,
-P(=O)(R^{18a})$_2$, or

 ;

R^{18a} is selected from:

C_1-C_8 alkyl substituted with 0-2 R^{19},
C_2-C_8 alkenyl substituted with 0-2 R^{19},
C_2-C_8 alkynyl substituted with 0-2 R^{19},
C_3-C_8 cycloalkyl substituted with 0-2 R^{19},
aryl substituted with 0-4 R^{19},
aryl(C_1-C_6 alkyl)- substituted with 0-4 R^{19},

a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N,

said heterocyclic ring being substituted with 0-4 R^{19},

C_1-C_6 alkyl substituted with a 5-10 membered heterocyclic ring system having 1-3 heteroatoms selected independently from O, S, and N, said heterocyclic ring being substituted with 0-4 R^{19};

R^{18b} is selected from R^{18a} or H;

R^{19} is selected from H, halogen, CF_3, CN, NO_2, $NR^{12}R^{13}$, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{11} cycloalkyl, C_4-C_{11} cycloalkylalkyl, aryl, aryl(C_1-C_6 alkyl)-, C_1-C_6 alkoxy, or C_1-C_4 alkoxycarbonyl;

Y is selected from hydroxy, C_1 to C_{10} alkyloxy, C_3 to C_{11} cycloalkyloxy, C_6 to C_{10} aryloxy, C_7 to C_{11} aralkyloxy, C_3 to C_{10} alkylcarbonyloxyalkyloxy, C_3 to C_{10} alkoxycarbonyloxyalkyloxy, C_2 to C_{10} alkoxycarbonylalkyloxy, C_5 to C_{10} cycloalkylcarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonyloxyalkyloxy, C_5 to C_{10} cycloalkoxycarbonylalkyloxy, C_7 to C_{11} aryloxycarbonylalkyloxy, C_8 to C_{12} aryloxycarbonyloxyalkyloxy, C_8 to C_{12} arylcarbonyloxyalkyloxy, C_5 to C_{10} alkoxyalkylcarbonyloxyalkyloxy, C_5 to C_{10} (5-alkyl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, C_{10} to C_{14} (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyloxy, $(R^2)(R^3)N$-(C_1-C_{10} alkoxy)-;

m is 0-2;

n is 0-2; and

p is 1-5.

48. A method of treating rheumatoid arthritis, asthma, allergies, adult respiratory syndrome, organ transplantation rejection, septic shock, psoriasis, contact dermatitis, osteoporosis, osteoarthritis, tumor metastasis, diabetic retinopathy, inflammatory conditions and inflammatory bowel disease, comprising administering

to a host in need of such treatment a therapeutically effective amount of a compound of Claim 47.

49. A pharmaceutical composition for intranasal administration, said composition comprising a therapeutically effective amount of a compound of Claim 1-28 or 45-47, a pharmaceutically acceptable excipient, and water.

50. A method of administering a compound of Claim 1-28 or 45-47, said method comprising intranasally administering, to a patient in need of such treatment, a therapeutically effective amount of a pharmaceutical composition containing said compound.

51. A compound of Claim 35 wherein the pharmaceutically acceptable salt form is selected from: hydrochloride, benzenesulfonate, methanesulfonate, or para-toluenesulfonate.

52. A prodrug ester of a compound of Claim 37, wherein the pharmaceutically acceptable salt form is selected from: acetate, methanesulfonate, hydrochloride, benzenesulfonate, or para-toluenesulfonate.

INTERNATIONAL SEARCH REPORT

Inter[redacted]pplication No
PCT[redacted]6/07692

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D261/04 A61K31/42 C07D261/10 C07D498/10 C07D413/04
C07D413/10 C07D413/06 C07D413/14 C07D413/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 35, no. 23, 13 November 1992, pages 4393-4407, XP000561169 ALIG L ET AL: "LOW MOLECULAR WEIGHT, NON-PEPTIDE FIBRINOGEN RECEPTOR ANTAGONISTS" see the whole document ---	1,6,11, 16,20, 24, 29-34, 48-50
A	WO,A,94 08577 (MERCK & CO INC) 28 April 1994 see claims ---	1,6,11, 16,20, 24, 29-34, 48-50

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 1996	- 7. 08. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 525 629 (THOMAE GMBH DR K) 3 February 1993 cited in the application see claims ---	1,6,11, 16,20, 24, 29-34, 48-50
A	US,A,5 227 490 (HARTMAN GEORGE D ET AL) 13 July 1993 see claims ---	1,6,11, 16,20, 24, 29-34, 48-50
A	EP,A,0 478 328 (MERCK & CO INC) 1 April 1992 cited in the application see claims ---	1,6,11, 16,20, 24, 29-34, 48-50
A	EP,A,0 512 831 (MERCK & CO INC) 11 November 1992 cited in the application see claims ---	1,6,11, 16,20, 24, 29-34, 48-50
P,X	WO,A,95 14683 (DU PONT MERCK PHARMA) 1 June 1995 see claims ---	1-50
P,X	WO,A,95 14682 (DU PONT MERCK PHARMA) 1 June 1995 see claims -----	1-50

2

INTERNATIONAL [redacted]RCH REPORT

Inte[redacted]plication No.
PCT/US[redacted]07692

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 29,31-31,48-50 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The definition of the substituents is too general and is only partly supported by the examples. Guided by the spirit of the application the search was carried out on the basis of the examples (CF Art. 6, Guidelines Exam Part.B Chapt. III, 3.6, 3.7). Claims searched incompletely: 1-4,6-9, 11-13, 10-18, 20-22, 24-27, 29-34, 39-52

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

Inter[redacted]ication No
PCT/[redacted]/07692

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9408577	28-04-94	AU-B- 5357894	09-05-94
		CA-A- 2144762	28-04-94
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